

# NEW SYNTHETIC METHODOLOGIES BASED ON COBALT (II) CATALYZED ORGANIC TRANSFORMATIONS

*A Thesis Submitted  
in Partial Fulfilment of the Requirements  
for the Degree of  
DOCTOR OF PHILOSOPHY*

*by*  
**M. MADHAVA REDDY**

*to the*

**DEPARTMENT OF CHEMISTRY  
INDIAN INSTITUTE OF TECHNOLOGY KANPUR  
February 1994**

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*Dedicated  
To  
My Parents*

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## STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India under the supervision of Prof. Javed Iqbal.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made whereverver the work described is based on the findings of other investigators.



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Kanpur

February, 1994.

**DEPARTMENT OF CHEMISTRY  
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**CERTIFICATE-I**

This is to certify that **Mr. M. Madhava Reddy** has satisfactorily completed all the courses required for the Ph.D. degree programme. These courses include :

CHM 605 Principles of Organic Chemistry

CHM 625 Principles of Physical Chemistry

CHM 645 Principles of Inorganic Chemistry

CHM 664 Modern Physical Methods in Chemistry

CHM 611 Physical Organic Chemistry

CHM 602 Advanced Organic Chemistry-II

CHM 800 General Seminar

CHM 801 Graduate Seminar

CHM 900 PG Research

**Mr. Madhav Reddy** successfully completed his Ph.D. qualifying examination in September, 1991.



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Sat. 28 Jan 1994

## CERTIFICATE-II

It is certified that the work contained in the thesis entitled "NEW SYNTHETIC METHODS BASED ON COBALT(II) CATALYZED ORGANIC TRANSFORMATIONS" has been carried out by Mr. M. Madhava Reddy under my supervision and the same has not been submitted elsewhere for a degree.

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Professor

Department of Chemistry  
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February, 1994.

## ABSTRACT

The work presented in this thesis discusses new methodologies based on cobalt(II) catalyzed organic transformations. The thesis is divided into four chapters and a brief summary is presented below.

### **CHAPTER - I : COBALT(II) CATALYZED CONVERSION OF ALLYLIC ALCOHOLS TO TRANSPOSED ALLYLIC AMIDES IN THE PRESENCE OF NITRILES : SCOPE AND MECHANISM.**

This chapter describes conversion of various secondary or tertiary allylic alcohols to the corresponding transposed allylic amides in the presence of catalytic quantity of cobalt(II) chloride and acetic anhydride in acetonitrile. Tertiary alcohols undergo complete rearrangement whereas the secondary ones afford a mixture of regioisomers. Moderate yield of amides are also obtained by reacting acrylonitrile with secondary alcohols in 1,2-dichloroethane. The presence of acetic anhydride or acetic acid is quite crucial to the formation of amides as the absence of the former affords no amides and the allylic alcohols are mainly recovered as regioisomeric mixtures. The stereochemical studies using carvoyl alcohol indicates that these reactions are proceeding via a  $\pi$ -allyl complex rather than a [3,3] sigmatropic rearrangement of acetamide obtained in a Pinner reaction.

### **CHAPTER - II : COBALT(II) CATALYZED THREE COMPONENT COUPLING INVOLVING KETONES OR KETOESTER, ALDEHYDES AND ACETONITRILE : A NOVEL ONE POT SYNTHESIS OF $\beta$ -ACETAMIDO KETONES.**

This chapter describes a one pot synthesis of  $\beta$  -acetamido ketones from carbonyl compound, an aldehyde, acetyl chloride and acetonitrile in the presence of catalytic amount of cobalt(II) chloride. A variety of aromatic aldehydes were found to undergo a three component coupling to yield  $\beta$  -acetamido ketone in very good yield. The reaction of various 1,3-dicarbonyl compounds and ketones with aldehydes were explored and they were found to undergo highly selective formation of  $\beta$  -acetamido ketones. This methodology has been

developed for the synthesis of 1,3-aminoalcohols, an important precursor for a wide range of natural products. The reactivity of aliphatic aldehydes is also explored in the absence of ketones and it is found that the former can be converted to corresponding vinyl amides. A catalytic cycle has been proposed for these transformations which involves the intermediacy of  $\alpha$ -chloro acetate and cyclic azadioxo cations.

### **CHAPTER - III : COBALT(II) CATALYZED ALLYLATION OF 1,3-DICARBONYL COMPOUNDS WITH ALLYL ACETATES.**

This chapter describes the cobalt(II) catalyzed allylation of 1,3-dicarbonyl compounds with allyl acetates. A wide range of allyl acetates readily react with methyl acetoacetate, acetylacetone and ethyl 2-oxo-cyclopentanone carboxylate to give high yields of allylated products. The reaction with acetyl acetone is highly regioselective as compared to methyl acetoacetate and ethyl 2-oxo-cyclopentanone carboxylate. This methodology is better than palladium or molybdenum catalyzed allylations as it does not involve the mandatory formation of anions of 1,3-dicarbonyl compounds. We proposed a mechanism which involves intramolecular reaction between the cobalt enolate of 1,3-dicarbonyl compound and the complexed allyl ligand.

### **CHAPTER - IV : COBALT(II) CATALYZED SYNTHESIS AND REACTIONS OF EPOXIDES.**

The chemistry described in this chapter is divided into two parts. The first part describes the epoxidation of olefins with molecular oxygen in the presence of cobalt catalyst and 2-methyl propanal. Thus a wide range of olefins can be selectively epoxidized in high yields. Similarly, dienes and triene can be selectively monoepoxidized in moderate to good yields. A mechanism has been proposed for these transformations which occur via an acyl radical type of intermediate.

The second part of the chapter deals with cobalt catalyzed cleavage of epoxides with heteroatom bonded to trimethylsilyl group. Thus various epoxides can be regioselectively cleaved with trimethylsilyl azide and trimethyl silyl thiocyanate in very high yields. The important aspect of this methodology is that trimethyl silyl reagents are generated *in situ* by an

exchange reaction of chlorotrimethylsilane with sodium azide or sodium thiocyanate respectively. Moderate to good selectivity was observed using azide and thiocyanato trimethylsilane in the cleavage of epoxides. The role of cobalt is discussed which ionizes the TMS - X to a trimethylsilyl cation and the latter helps in the cleavage by coordination with the oxygen atom of epoxides.

## Acknowledgements

*The joy of discovery, which I felt in every step during the course of this study, fills my heart with gratitude for all those who have encouraged me with words, deeds and silent prayers and have sustained me during this period of ordeal.*

*The able guidance of my thesis supervisor Prof. Javed Iqbal gave me a sense of direction for the present study and instilled me in the desire to strive for perfection. The amount of freedom and independence with which he allowed me to work enabled me to have a wider perspective about the subject. I express my sincere gratitude to him. I also take this opportunity to express my gratitude to Mrs. Iqbal, Aman and Sarah for their love and affection showed on me.*

*I am grateful to Profs. S. Ranganathan, Parimal k. Bharadwaj, R.N. Mukherjee and Sathyamurthy for their valuable suggestions.*

*I would like to express my sincere gratitude to my guru Mr. P. Laxmi Narasimha Chary who taught me the early lessons during my school days and for his continued encouragement and inspiration even to this day.*

*Neither words nor thoughts can sustain me from expressing my feelings and gratitude to Dr. Naresh K. Nayyar who offered a helping hand without any hesitation at every stage of my research.*

*The warm and friendly attitude of my colleagues Beena, Maikap, Vibha, Pratibha, Punniyamurthy, Manoj, Bhasker, Swinder, Debraj and Biswas helped me to have a cheerful life in the lab. I extend my gratitude to them.*

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Last but not the least, I would like to express sincere gratitude to my parents, brothers and sisters who provided timely help and constant encouragement. Their aspirations and faith in me have buoyed me in my journey of life. Words can not express the depth of my love and respect towards them.

*Life is real , life is earnest.*

*And the grave is not its goal*

*Dust thou art, to dust returnest .*

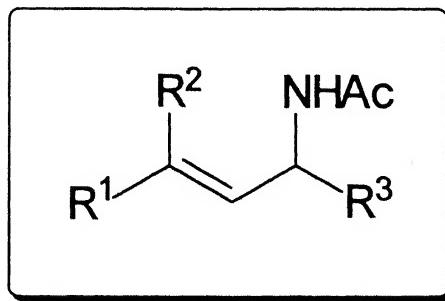
*Was not spoken of the soul.*

*-LONGFELLOW*

# Chapter 1

## COBALT(II) CATALYZED CONVERSION OF ALLYLIC ALCOHOLS TO TRANSPOSED ALLYLIC AMIDES IN THE PRESENCE OF NITRILES : SCOPE AND MECHANISM.

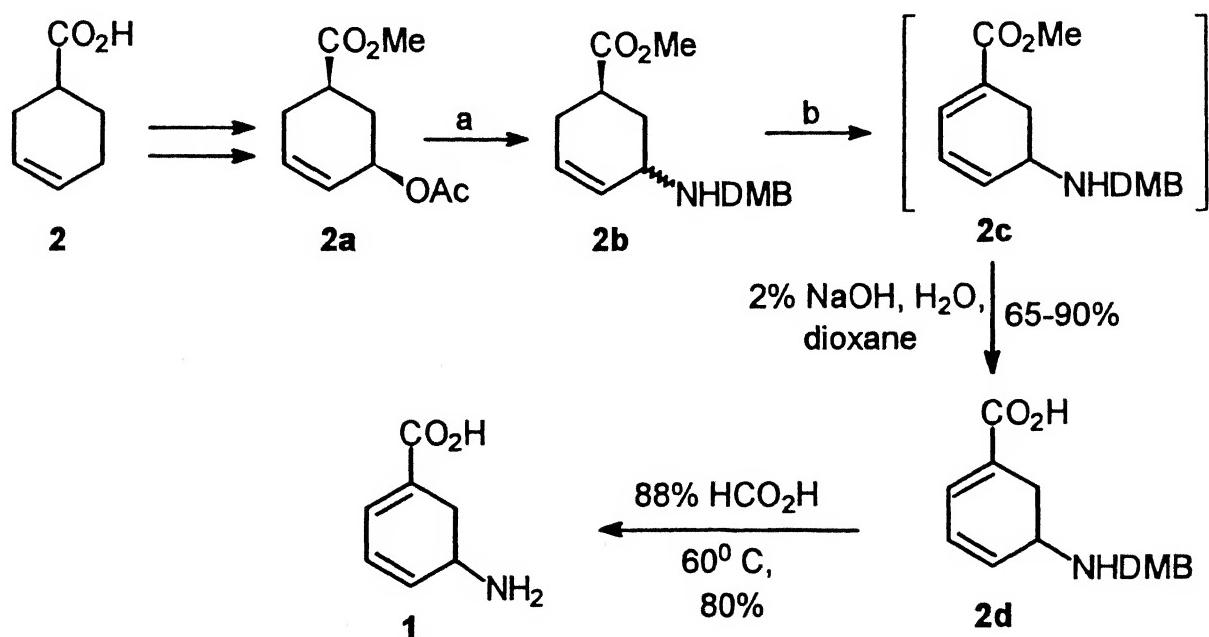
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## 1.1 INTRODUCTION

Allylic amides are important precursors for the synthesis of many naturally occurring allylic amines and amino acids<sup>1</sup>. The allylic amine moiety, mainly in primary allylic amines, has been shown to be biologically important. Thus, compounds embodying this function have been found to be inhibitors of several enzymatic systems : (i) Gamma amino butyro Transaminase, for example, Gabaculine, affect the neurotransmitter GABA ( $\gamma$ - amino butyric acid); (ii) Monoamine oxidase, where 2-phenyl-2-propenyl amines exhibit physiological activity; (iii) Squalene epoxidase, where a series of allyl amines have antifungal properties; and (iv) Angiotensin converting enzyme, where terpenic amines are incorporated in active inhibitors.

Naturally occurring amino acid ( $\pm$ )-Gabaculine **1** was first isolated by Mishima and coworkers from *Streptomyces toyocaensis*, is an inhibitor of  $\gamma$ -amino butyrate aminotransferase, an enzyme that is involved in the metabolism of GABA an important inhibitory transmitter in the nervous system<sup>3,4</sup>. Trost and coworkers<sup>5-7</sup> have synthesized the ( $\pm$ )-Gabaculine **1** from 3-cyclohexenecarboxylic acid **2** in 45% overall yield (Scheme 1.1)

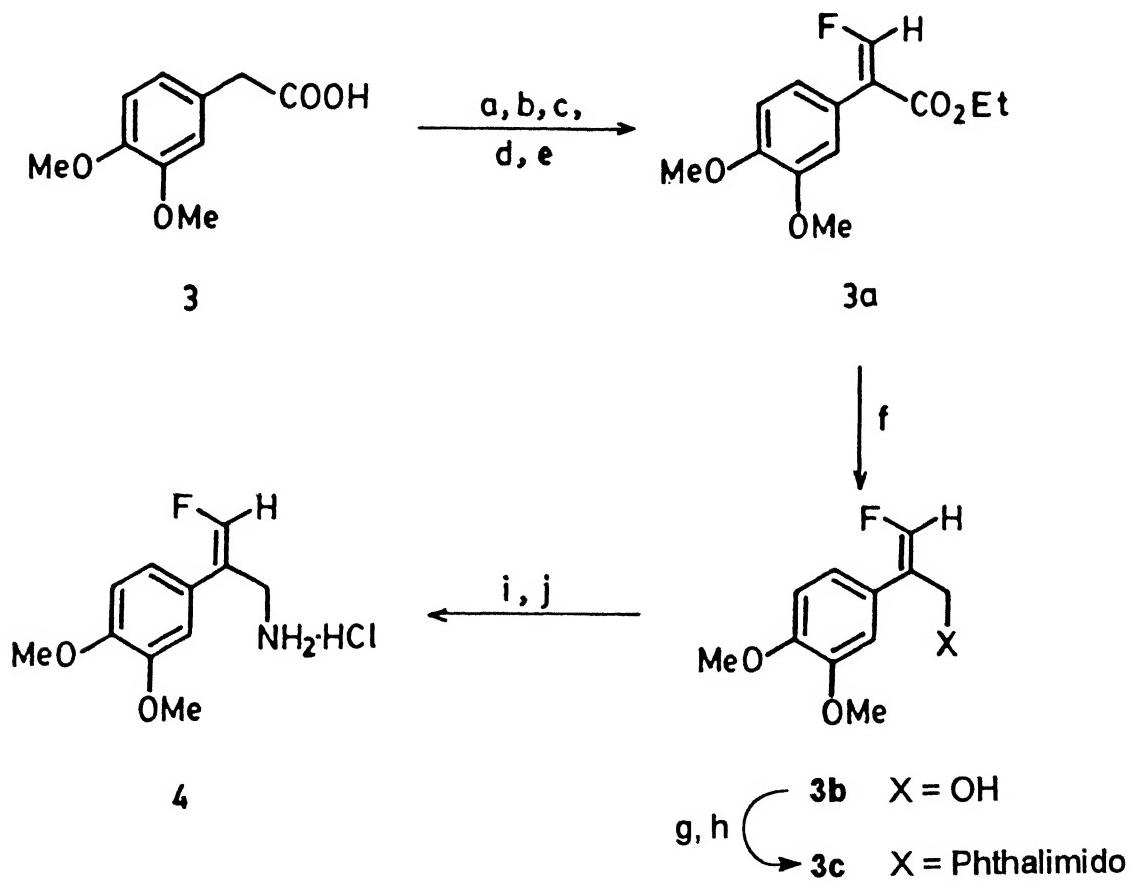


a) 4,4' - dimethoxy benzhydrylamine (DMB),  $(PPh_3)_4Pd$ , THF, ref.

b) (i) LDA, THF, -78° C and then I<sub>2</sub>   (ii) DABCO

Scheme 1.1

Inhibitors of monoamine oxidase (MAO) are effective antidepressants. McDonald and coworkers<sup>8</sup> have synthesized (E)-2-(3,4-dimethoxy phenyl)-3-fluoro allylamine derivatives **4** which are potent enzyme - activated irreversible inhibitors of MAO. These were prepared from the commercially available 3,4-dimethoxy phenyl acetic acid **3** (Scheme 1.2).

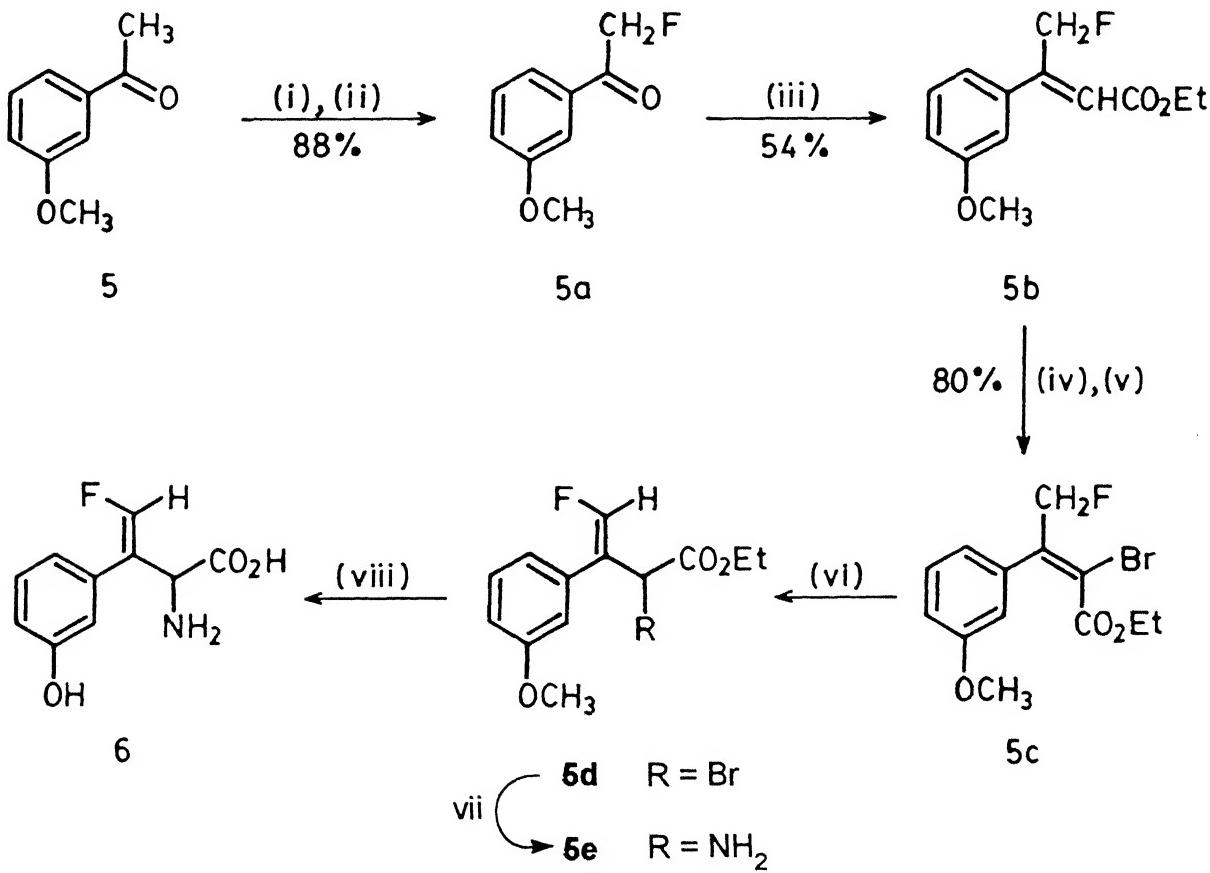


- a) t - butyl acetate,  $\text{HClO}_4$  ; b) LDA,  $\text{CICO}_2\text{Et}$  ; c)  $\text{Na}^+ \text{O}^- \text{But}$ ,  $\text{ClCHF}_2$  ; d)  $\text{CF}_3\text{CO}_2\text{H}$  ;  
e)  $\text{NaOH}$  ; f) DIBAL ; g)  $\text{PBr}_3$  ; h) Potassium phthalimide ; i)  $\text{NH}_2\text{NH}_2$  ; j)  $\text{HCl}$ .

**Scheme 1.2**

These authors have also reported<sup>9</sup> the synthesis of (E)- $\beta$ -(Fluoromethylene)-m-tyrosine **6**, which is an enzyme - activated irreversible inhibitor of monoamine oxidase requiring activation by aromatic L-amino acid decarboxylase (AADC) (Scheme 1.3).

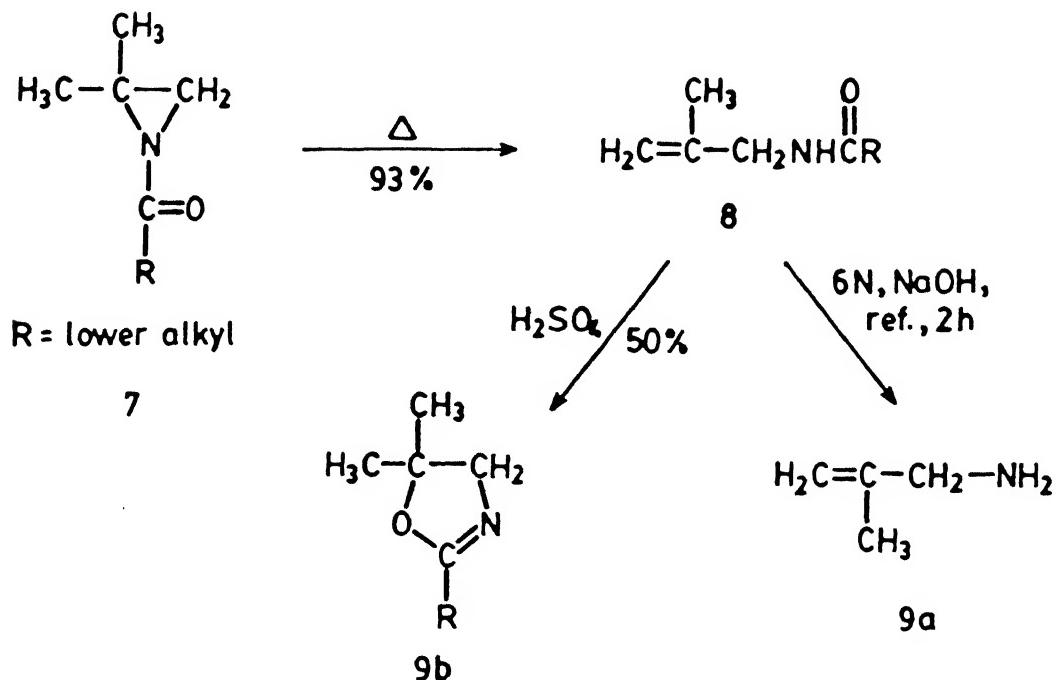
In view of the importance of these biologically active allylic amines, several methods have been developed<sup>10</sup> for the synthesis of allylic amides and amines.



- i)  $\text{Br}_2, \text{CHCl}_3, 0^\circ \text{C}, 3\text{h}$  ; ii)  $\text{KHF}_2$ , triethylene glycol,  $100^\circ \text{C}, 3\text{h}$  ;
- iii) triethylphosphono acetate,  $\text{NaH}$ , toluene,  $<15^\circ \text{C}, 30\text{min}$ .
- iv)  $\text{Br}_2, \text{CCl}_4, -5^\circ \text{C}, 3\text{h}$  ; v) piperidine, ether,  $5^\circ \text{C}, 2.5\text{h}$  ;
- vi) a)  $\text{LDA}, -78^\circ \text{C}, 30\text{min}$ . b)  $\text{H}^+, -78$  to  $0^\circ \text{C}$  ;
- vii) a)  $\text{NH}_3, \text{DMSO}, \text{r.t.}, 2.5\text{h}$  ; b)  $\text{HCl}$ , 20% overall yield from 5
- viii) a) aq.  $\text{HBr}$ , ref., 4h ; b)  ,  $\text{CH}_3\text{OH}$ , r.t., 3h. 86% yield

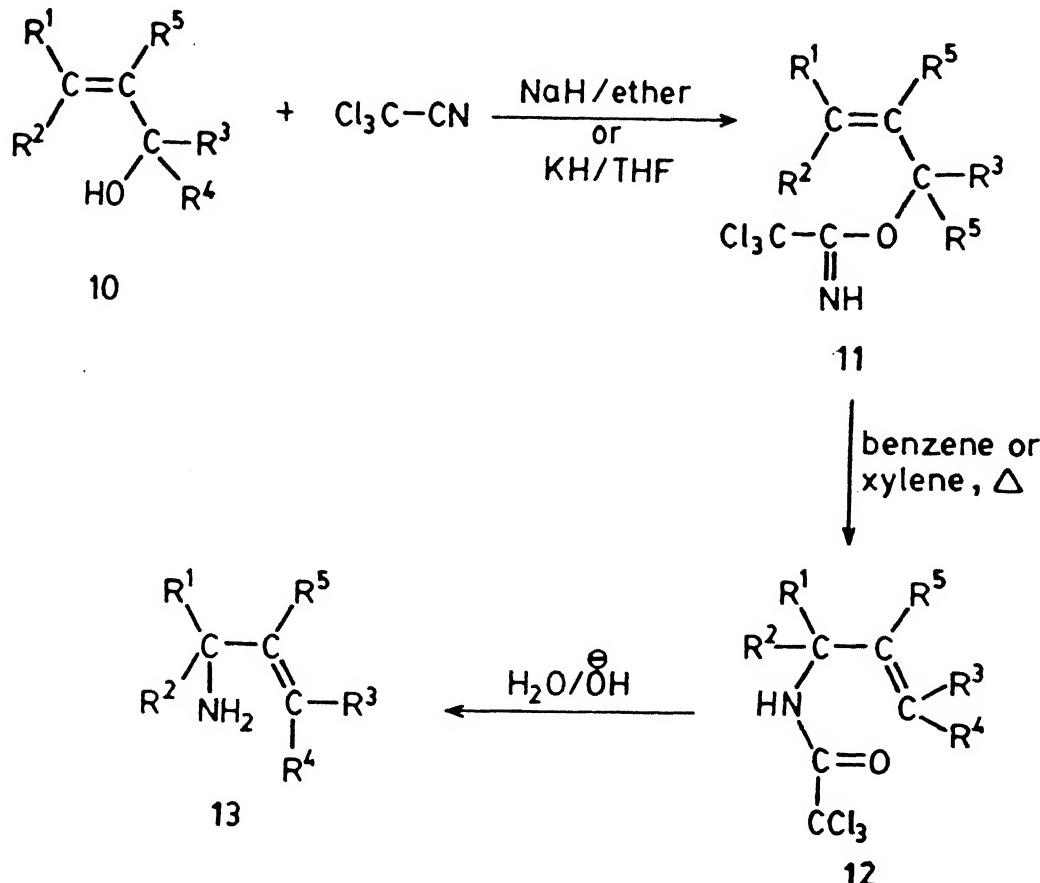
**Scheme 1.3**

In 1958, Fanta and Deutsch<sup>11</sup> have synthesized the allylic amides **8** by pyrolytic ring-opening reaction<sup>12-14</sup> of 1-acyl-2,2-dimethyl ethyl enimines **7**. These amides were characterized by alkaline hydrolysis to  $\beta$ -methallylamines **9a** and by acid catalyzed cyclization to 2,5,5-trimethyl-2-oxazoline **9b** (Scheme 1.4).

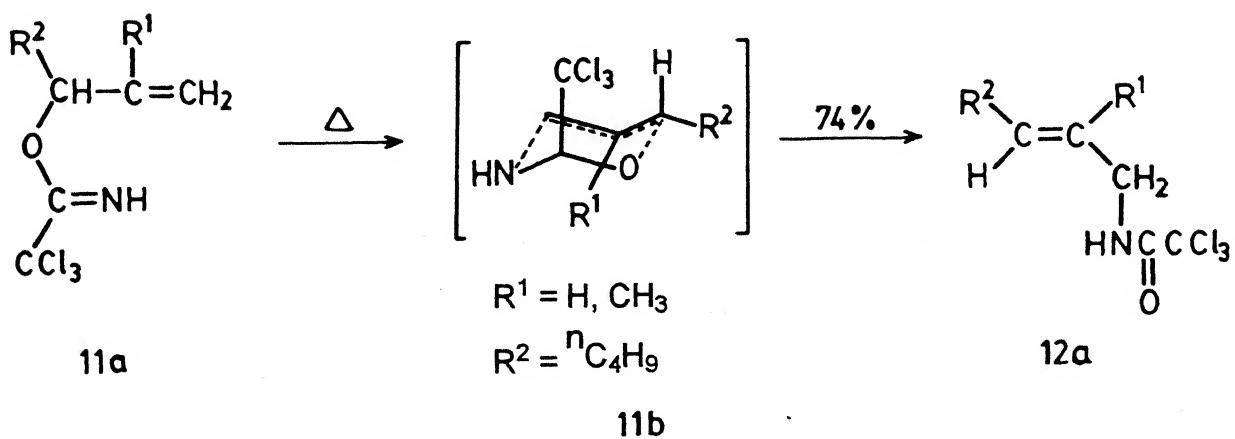
**Scheme 1.4**

Allylic amides can also be synthesized from allylic alcohols by displacement of the hydroxy group by nitriles.

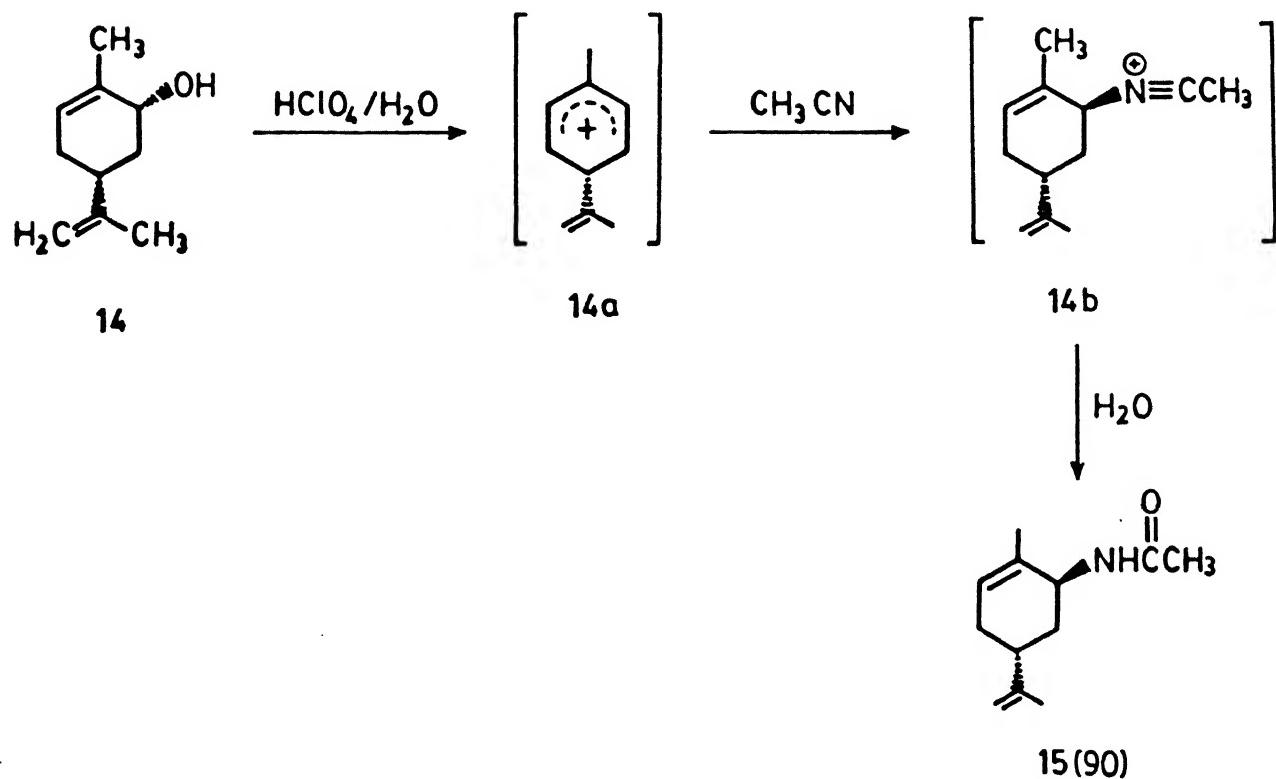
The imidic ester (or imidate) to amide rearrangement converts a carbon-oxygen to a carbon-nitrogen single bond<sup>15</sup>. Overman<sup>16,17</sup> has reported the synthesis of allylic amines **13** by *thermal rearrangement* of allylic trichloroacetamides **12**. This method, which is based on the [3,3]-sigmatropic rearrangement of allylic trichloroacetamides involves three steps. First, the base catalyzed addition of trichloroacetonitrile to the allylic alcohol **10** affords the trichloroacetamide **11** in quantitative yield. The key step in synthesis is the thermal rearrangement of the allylic imidate **11** which allows the formation of a carbon-nitrogen bond. Finally, the acetyl group was removed by treatment with 6N NaOH in ethanol at room temperature (Scheme 1.5). The reaction is regiospecific, transposed amide is exclusively obtained. Moreover, this reaction is stereoselective, since it preferentially leads to the (E)-isomer.

**Scheme 1.5**

The stereoselectivity observed in the formation of substituted alkenes is similar to that observed for other [3,3]-sigmatropic rearrangements. This stereoselectivity can be expected from the large steric bulk of the trichloromethyl substituent and the usual chair model for the cyclic six-membered transition state<sup>18-20</sup> (Scheme 1.6).



Allylic acetamides can be prepared by the reaction of allylic alcohols with perchloric acid in acetonitrile<sup>21</sup>. For instance, cis- carveol **14** is reacted to give the corresponding trans-amide **15** in 90% yield (Scheme 1.7).



**Scheme 1.7**

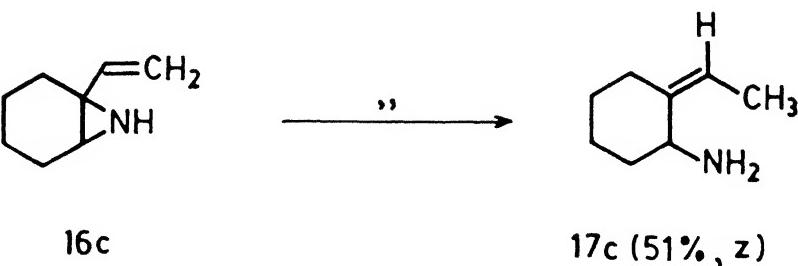
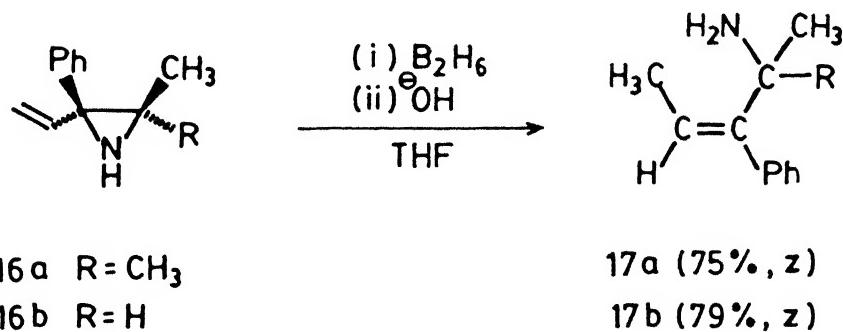
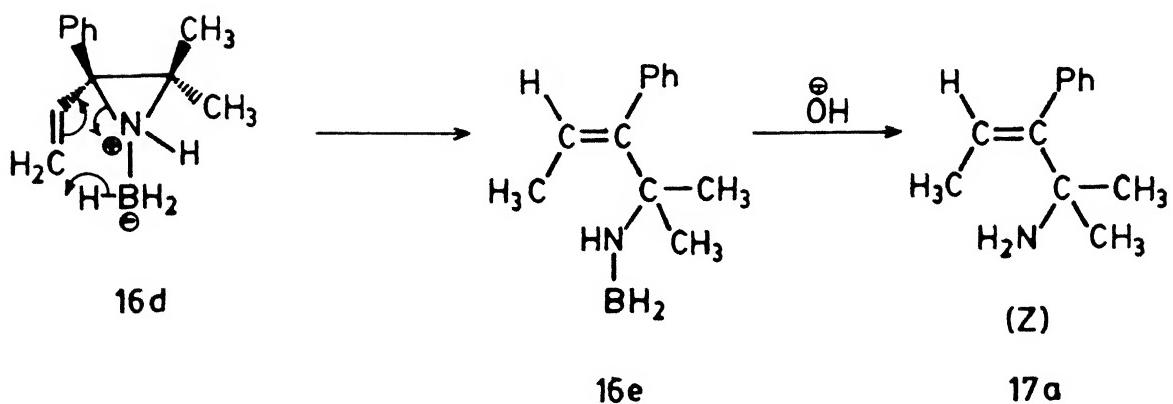
This Ritter reaction is, however, of little practical value: the intermediate carbocations are generally prone to side reactions.

Reaction of 2-vinylaziridines<sup>22–24</sup> **16** with diborane in THF afforded the  $\alpha$ -substituted allylic amines **17** in good yields (Scheme 1.8).

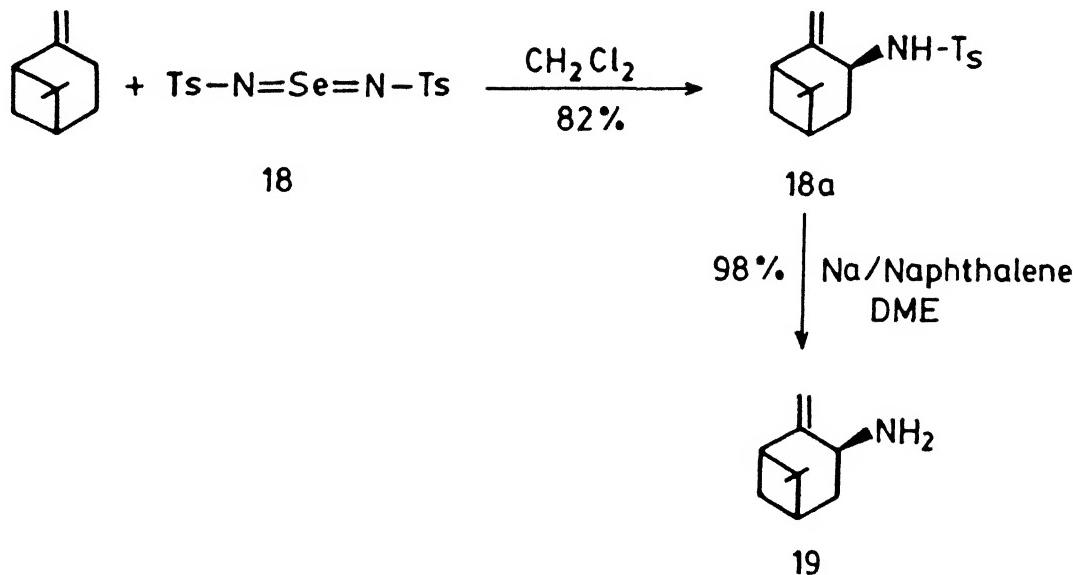
This reaction is regiospecific as only Z-isomer is obtained. The mechanism involves the formation of complex **16d** which undergoes internal hydride transfer to give aminoborane **16e**. Base hydrolysis of this intermediate affords the amine **17a** (Scheme 1.9).

It was found<sup>25–27</sup> that aza analogues **18** of selenium dioxide effect allylic amination of olefins (Scheme 1.10).

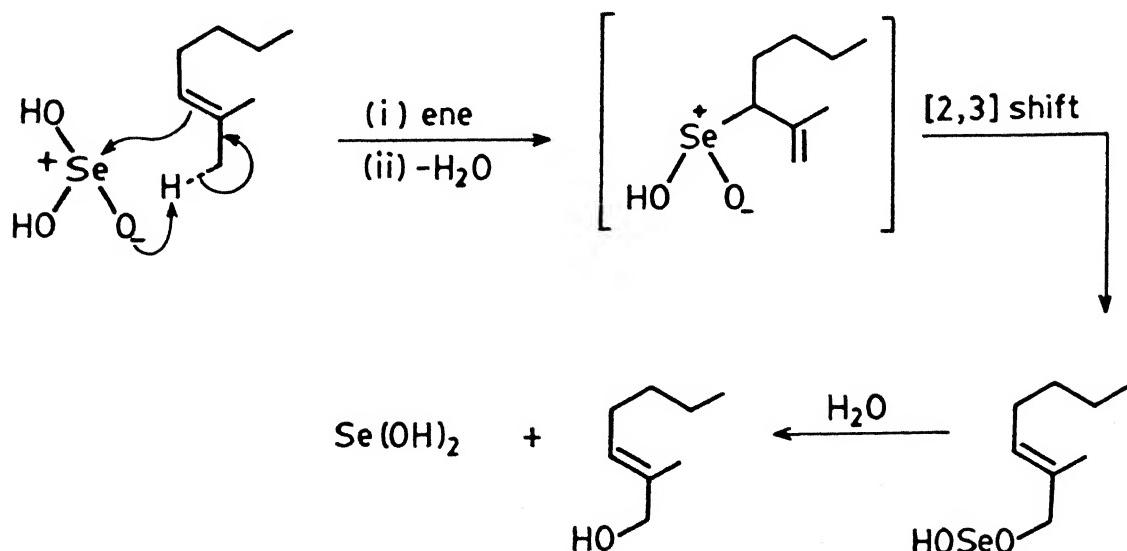
Imidoselenium compound **18** is obtained from the reaction of selenium tetrachloride with

**Scheme 1.8****Scheme 1.9**

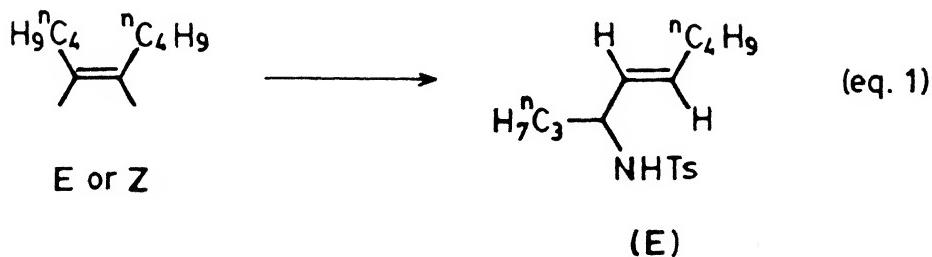
two equivalents of p-toluenesulfonamide in dichloromethane in the presence of four equivalents of an amine base. An even more reactive aminating species are formed when two equivalents of anhydrous chloramine T (TsNCINa) are stirred with selenium metal in dichloromethane. Due to its ease of preparation and superior reactivity, this chloramine T derived reagent was used

**Scheme 1.10**

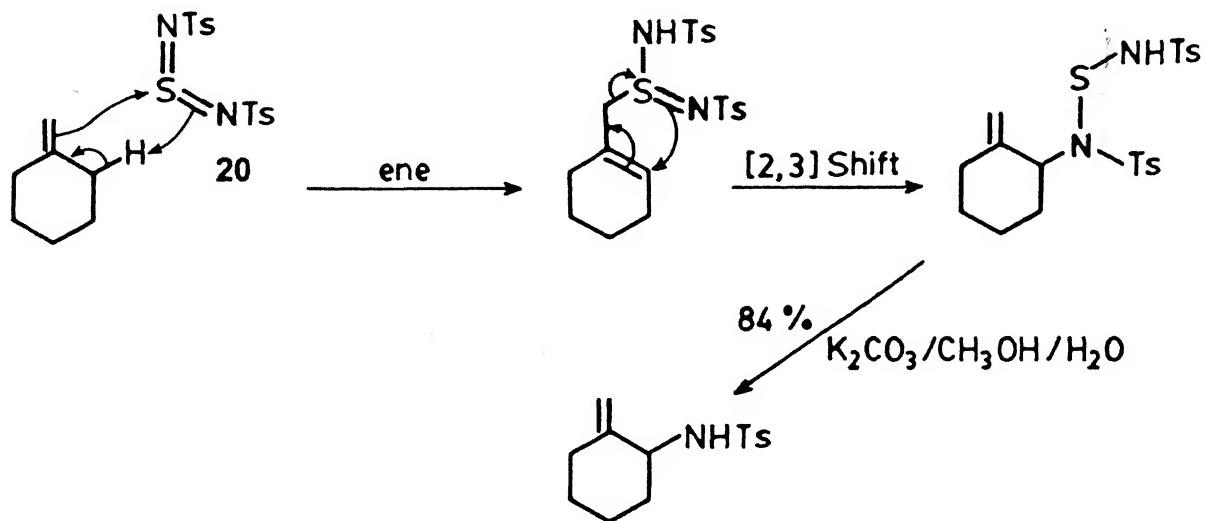
for amination. Nitrogen insertion takes place on the most substituted allylic carbon and the ease of oxidation is  $\text{CH}_2 \succ \text{CH}_3 \succ \text{CH}$ . These aminations occur via the ene and [2,3]-sigmatropic reactions<sup>28</sup> which is similar to the mechanism of the analogous oxoprocess (Scheme 1.11).

**Scheme 1.11**

The reaction is stereospecific as the E-isomer is obtained whatever the configuration of the starting alkene (eq. 1).



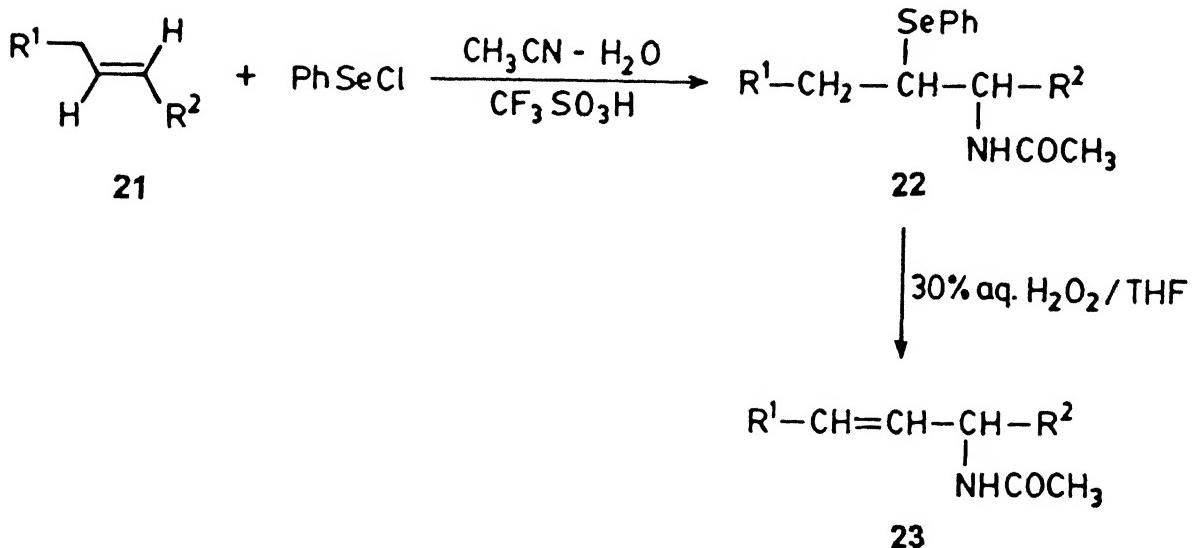
The sulfur diimide species **20** has been shown to be an excellent reagent for the allylic amination of olefins<sup>29</sup>. Although more difficult to prepare than the corresponding selenium compound<sup>25</sup>, the sulfur reagent **20** has the advantage over selenium reagent **18** as it gives very clean product in good yields (Scheme 1.12).



Scheme 1.12

The mechanism is same as described for the allylic amination of olefins with imido selenium compounds<sup>28</sup>. This methodology has been applied to a total synthesis of ( $\pm$ )-gabaculine.

Toshimitsu et al synthesized the allylic amides **23** by oxidation-fragmentation of  $\beta$ -amidoalkyl phenyl selenides **22**, which derived from the reaction of olefins **21** with PhSeCl in acetonitrile containing small amounts of organic acid and water in selective manner (Scheme 1.13).

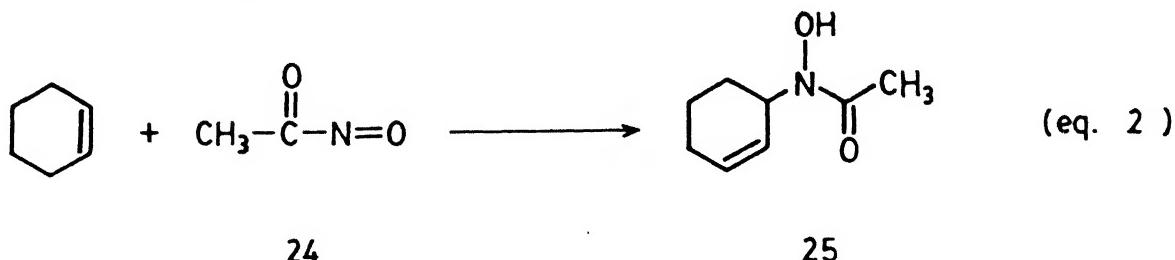


**Scheme 1.13**

Cis-2-butene gives the threo- product whereas the trans-isomer gives erythro compound. This elimination reaction proceeds with trans-stereospecificity.

Gary Keck and coworkers<sup>31</sup> have developed a versatile method for carbon-nitrogen bond formation via ene reactions<sup>32-34</sup> of acylnitroso compounds.

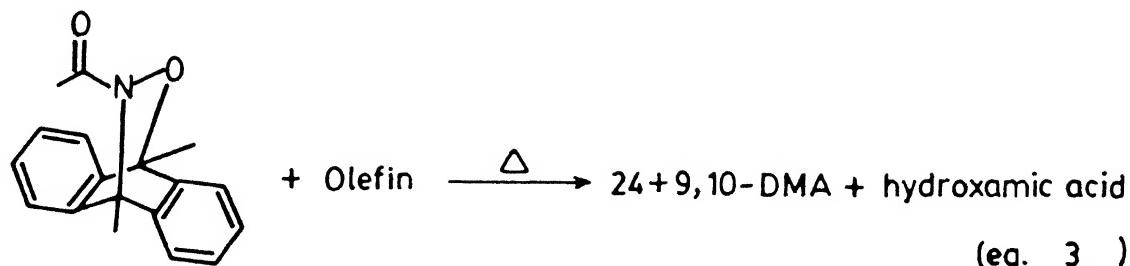
The bimolecular ene reaction of an acylnitroso moiety with simple olefins affords a method for effecting *allylic amidation*, as shown in eq. 2 below for the reaction of cyclohexene with



nitroso carbonylmethane **24**, affording an N-alkylhydroxamic acid which can be easily converted to the N-alkylacetamide **25**. This reaction proceeds, with allylic rearrangement and affords a product at the oxidation level of amide, rather than amine<sup>24,28</sup>.

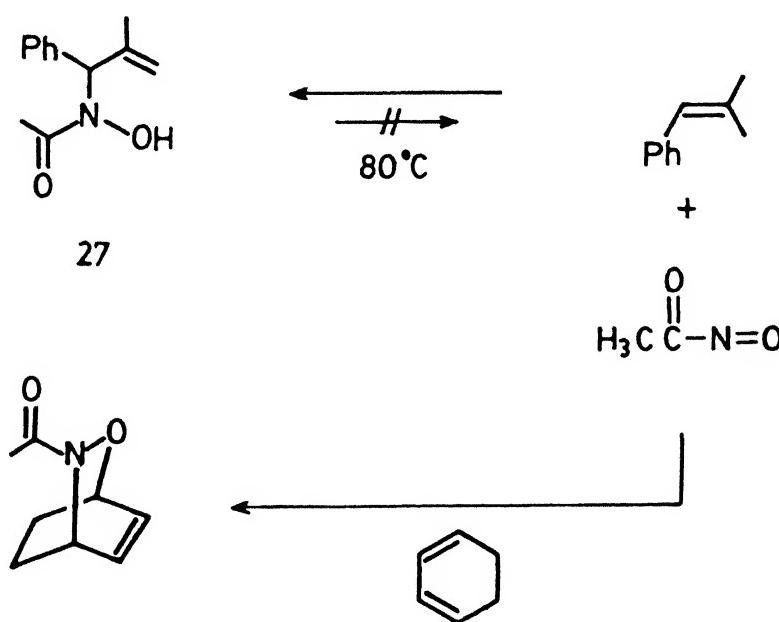
The highly reactive acylnitroso compounds **24** are generated *in situ* by pyrolysis of compound **26**<sup>35</sup> which can be prepared by oxidation of acetohydroxamic acid with N(Pr)<sub>4</sub> IO<sub>4</sub> in

the presence of 9,10-dimethylanthracene, which is stable at room temperature (eq. 3).



**26**

This ene reaction is regiospecific, involves a kinetically controlled process with a product determining stage of the reaction in which nitrogen adds to the olefin  $\pi$ -system to generate a species with significant free valence (odd electron density or positive charge) on carbon. This would then result in bonding of nitrogen to the less substituted unsaturated carbon. For example, the ene product **27**, from 2-methyl-1-phenylpropene, should be prone to reversal (Scheme 1.14). Thus phenyl conjugation is restored upon reversal of the ene reaction, and the

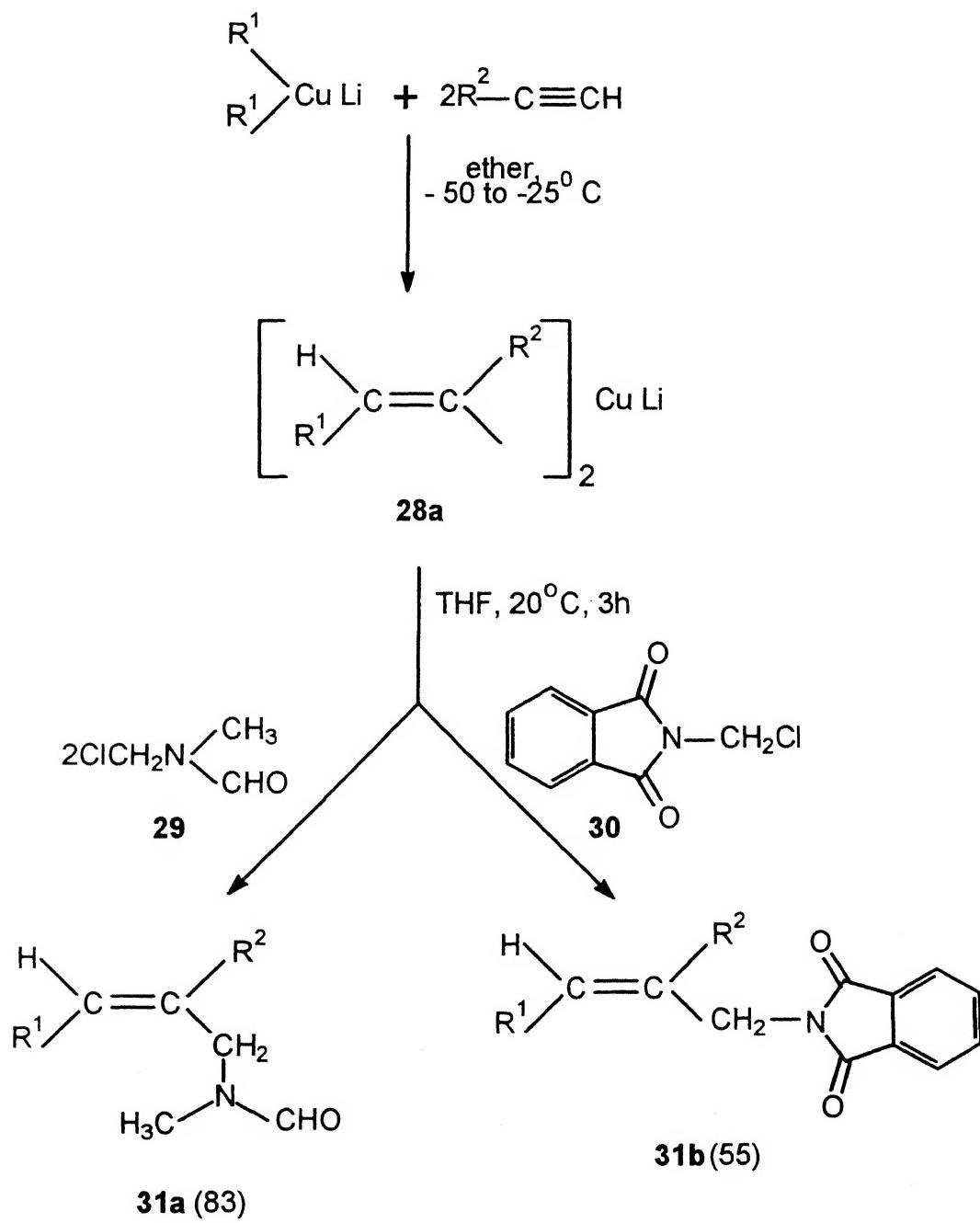


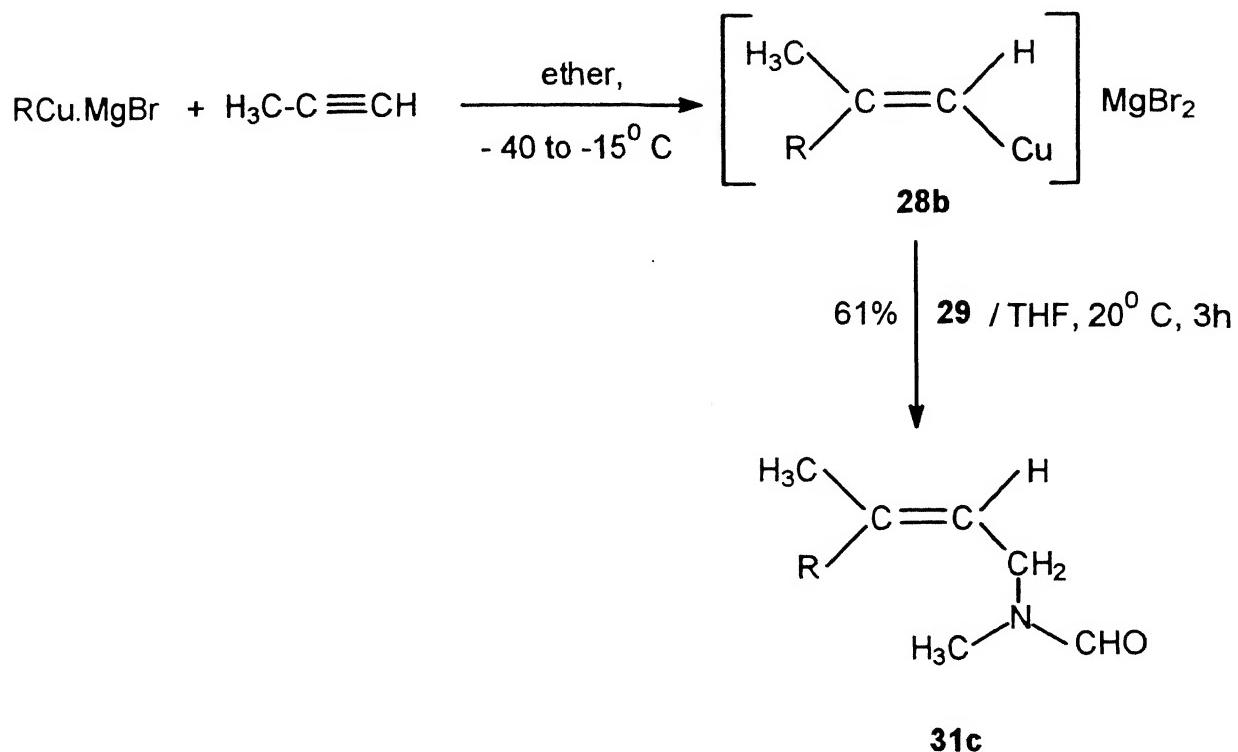
**Scheme 1.14**

C-N bond in **27**, being both allylic and benzylic, should be the weakest. But pyrolysis of **27** at  $80^\circ\text{C}$  in benzene in presence of 1.0 M cyclohexadiene, no retro-ene fragmentation was

discernible and **27** was recovered unchanged. This clearly indicates the kinetic controlled process of this ene reaction.

Alkenyl-cuprate and copper reagents<sup>36</sup> **28a** and **28b** are easily available by carbocupration of alkynes. These reagents react with N-chloromethyl-N-methyl formamide **29** and the commercially available N-chloromethyl phthalimide **30** to afford (*Z*)-allylic amides **31a-c** in high yields (Scheme 1.15).



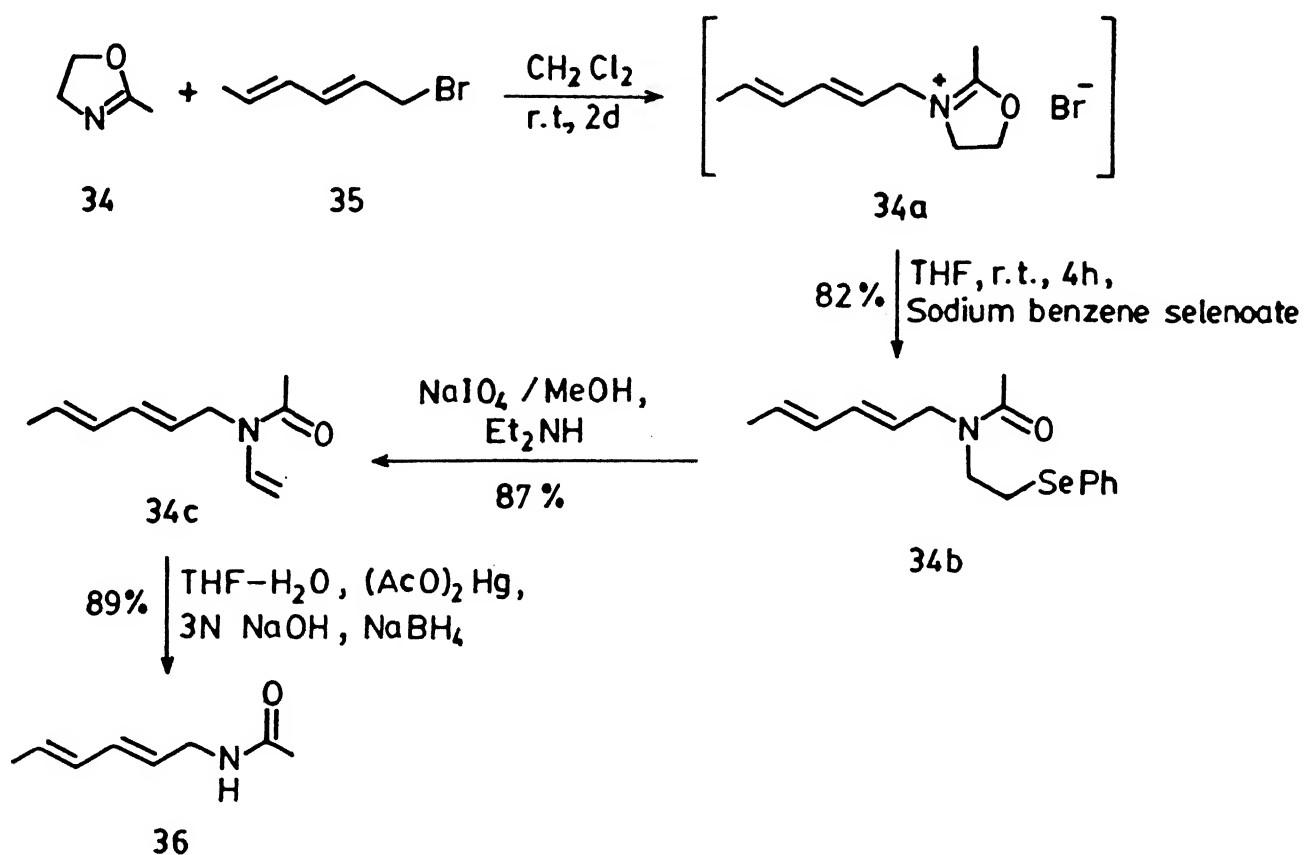


**Scheme 1.15**

Alkenyl-copper reagents associated with magnesium salts are totally unreactive towards the reagent **30**. However, they are transformed *in situ* into the more reactive unsymmetric cuprate **28c** by the addition of one equivalent of alkynyllithium reagent **32**. This cuprate **28c** couples with **30** to afford the polysubstituted allylic amide **33**.

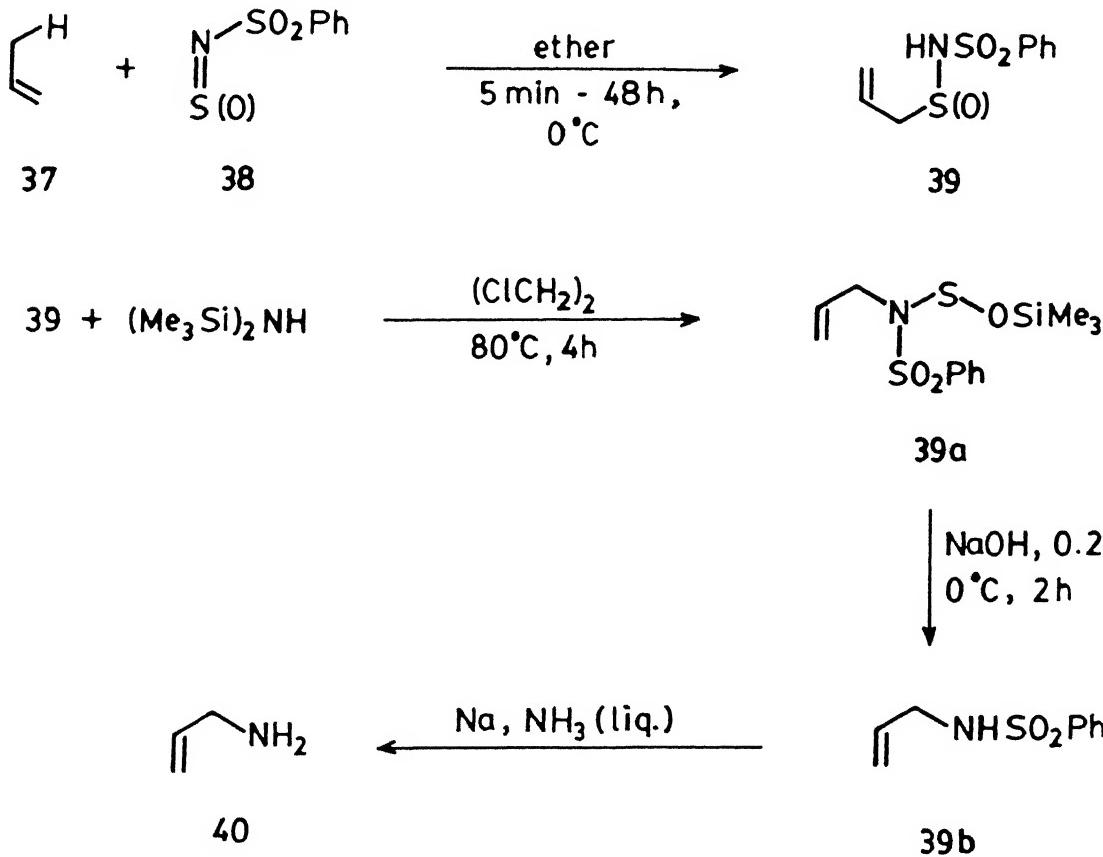
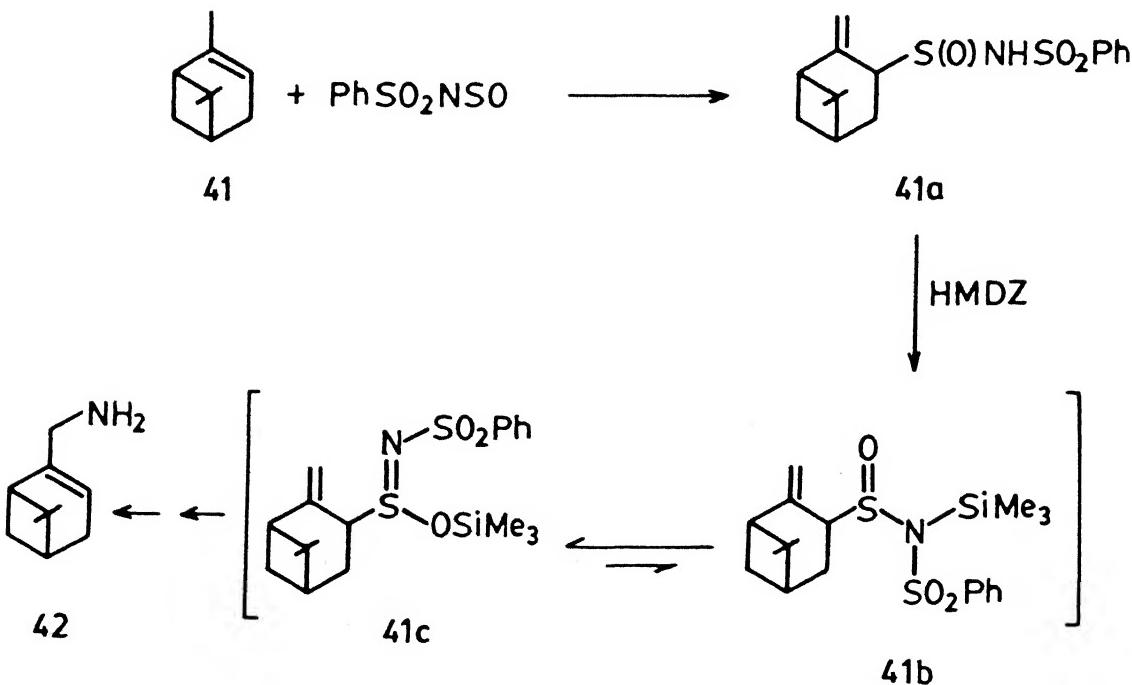
Secondary carboxamides<sup>37</sup> can be synthesized easily and efficiently by the reaction of 2-methyl-2-oxazoline **34** and 2,4-hexadienyl bromide **35**. N-(2,4-hexadienyl) acetamide **35** can be prepared as shown in the scheme 1.16.

This reaction involves three basic transformations : (i) initial carbon-nitrogen bond forming reaction between **34** and an appropriate halide; (ii) nucleophilic ring opening of the oxazine moiety **34a** by the use of sodium benzeneselenoate to effect the construction of carboxamide framework, and (iii) final splitting off of the 2-phenyl selenoethyl substituent on the nitrogen atom. Removal of vinyl group on N-atom (or devinylation) was carried out by oxymercuration-demercuration reaction.

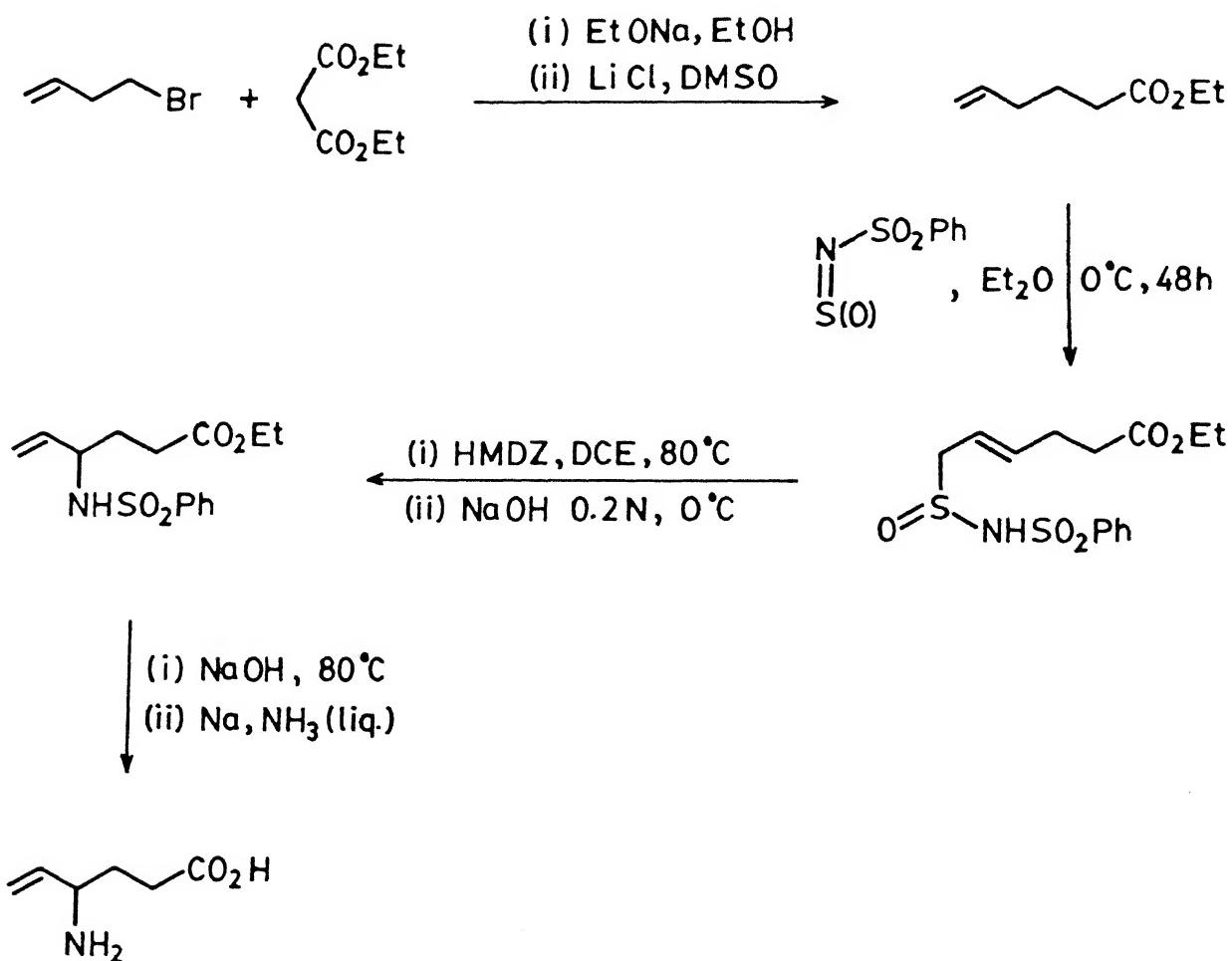
**Scheme 1.16**

Deleris et al.<sup>1</sup> have synthesized the allylic amines from olefins by *ene reaction*. As the reaction shown in Scheme 1.17, when olefin 37 is mixed with enophile 38 the adduct 39 was formed in ure form. A stoichiometric mixture of 39 and hexamethyldisilazane (HMDZ) was heated at 80° in DCE and when the resulting solution was treated with aqueous sodium hydroxide afforded the allylic amine 40 protected as the sulphonamide 39b. Deprotection of sulphonamide 39b by sodium in liquid ammonia yielded the allylic amine 40. For example, 42 was prepared from -pinene 41 as shown in the Scheme 1.18.

This methodology was applied for the synthesis of 4-amino 5-hexenoic acid 43 (Gamma vinyl GABA) which is a potent *suicide* inhibitor of GABA transaminase. GABA-T is a target enzyme involved in the metabolic degradation of the inhibitory neurotransmitter Gamma amino Butyric Acid. Thus Gamma vinyl GABA shows important clinical properties in the

**Scheme 1.17****Scheme 1.18**

treatment of several diseases such as Huntington disease or epilepsy<sup>38,39</sup>. The synthesis of 4-amino 5-hexenoic acid is shown in the Scheme 1.19.

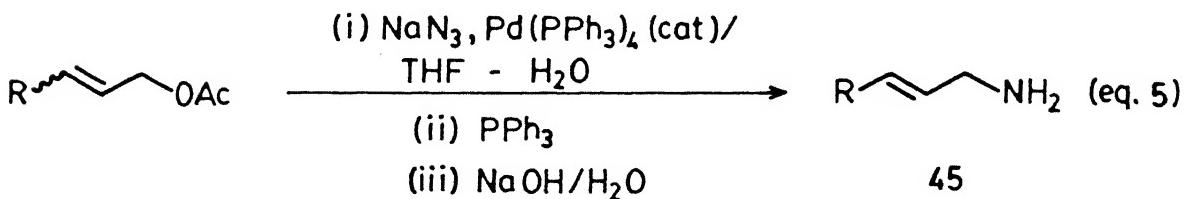
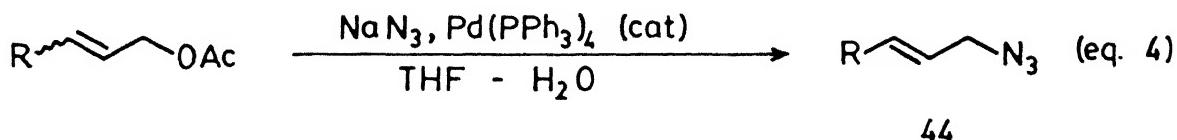


(overall yield 26.5% from ethylhexenoate)

**Scheme 1.19**

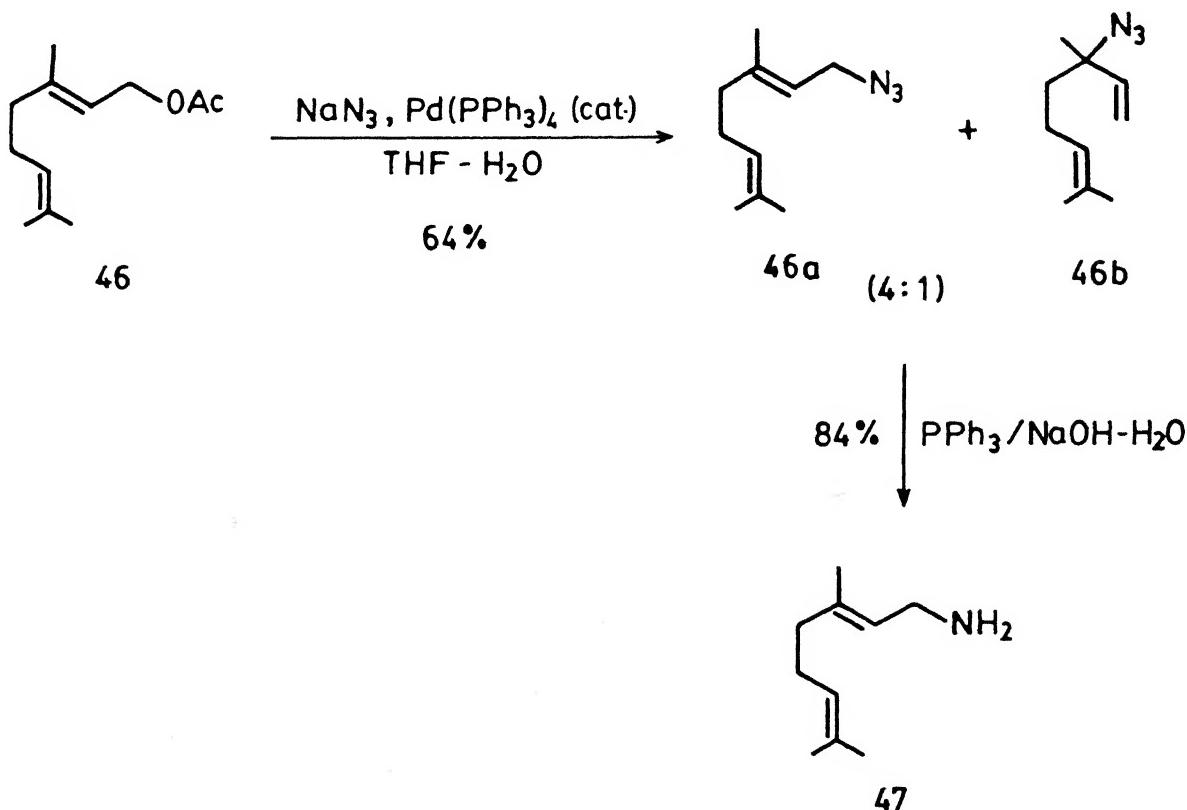
Palladium catalyzed amination of allylic compounds is an efficient method for the synthesis of various nitrogen containing biologically active compounds<sup>40–42</sup> such as alkaloids and amino sugars.

Palladium (O) catalyzed reaction of allyl acetates with azide ion<sup>43</sup> gives the corresponding allyl azides **44**, which are versatile synthetic intermediates<sup>44</sup> (eq. 4). These allyl azides can be readily converted into primary allylic amines **45** upon treatment with PPh<sub>3</sub>/NaOH without isolation (eq. 5).



It is noteworthy that,  $\pi$ -allyl palladium complexes react with azide ion, which is a borderline nucleophile in the HSAB principle.

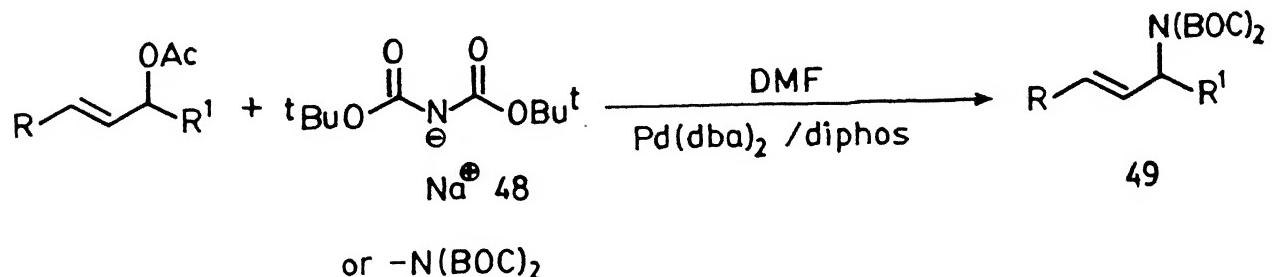
This reaction is highly useful for the preparation of primary (E)-allyl amines because of its high regioselectivity. Even a mixture of  $\alpha$ - and  $\gamma$ -allyl azides can be converted into the corresponding  $\alpha$ -allylamines. For example, a mixture of geranyl 46a and linalyl azide 46b, which derived from the azidation of geranyl acetate 46 upon treatment with  $\text{PPh}_3$  affords geranylamine 47 exclusively (Scheme 1.20).



**Scheme 1.20**

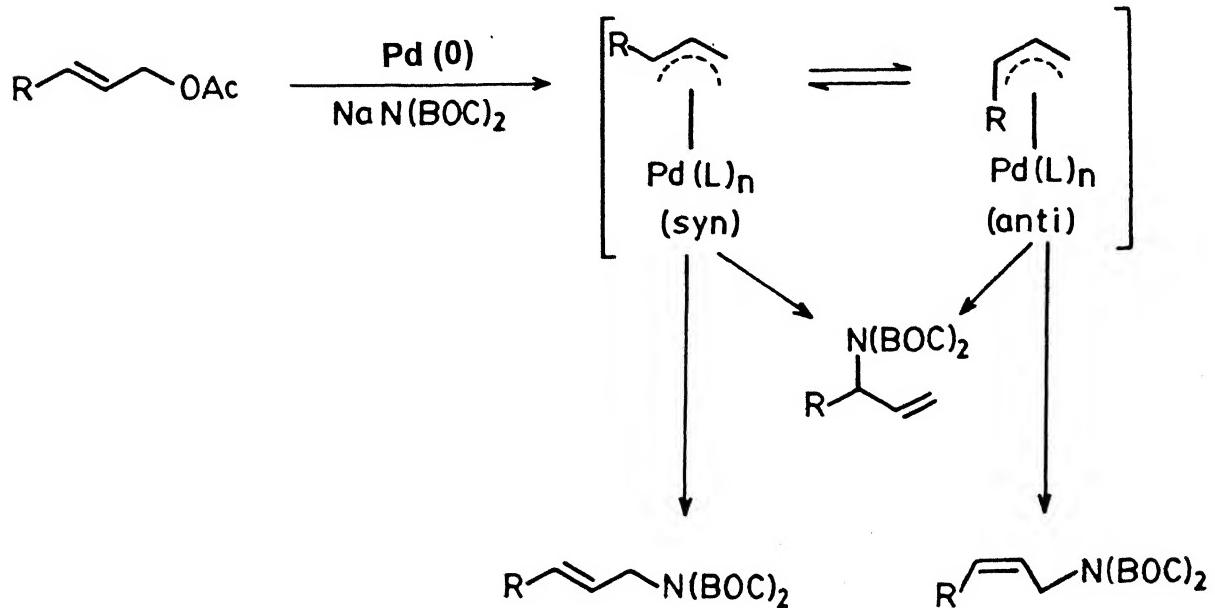
Palladium-catalyzed conversion of allylic acetates to the corresponding amines with phthalimide<sup>45</sup>, sodium azide<sup>43</sup>, p-toluene-sulfonamide<sup>46</sup> and 4,4'-dimethoxybenzhydrylamine<sup>5</sup> as nucleophiles involves multistep reactions. Paul Helquist and coworkers<sup>47</sup> have developed a direct method for the conversion of allylic acetates into suitably protected primary amines.

When the sodium or potassium salt of di-*tert*-butyl iminodicarbonate **48** was added to a warm DMF solution of allyl acetate, a diprotected amine **49** was obtained as shown in the Scheme 1.21.



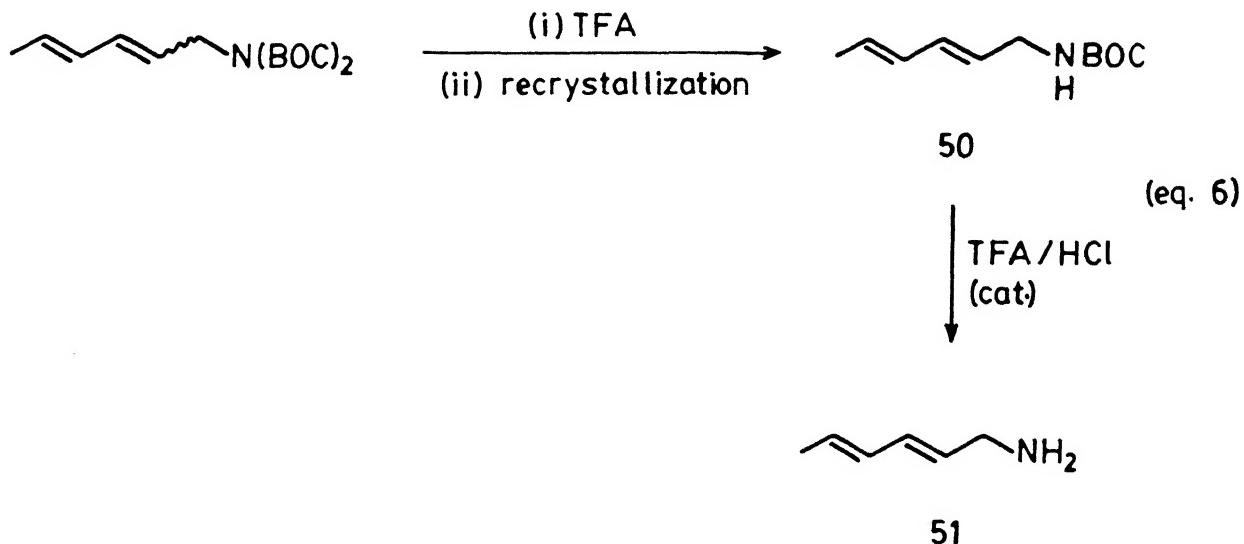
**Scheme 1.21**

These products may all be derived from the  $\pi$ -allyl intermediate which can be attacked at either the C-1 or C-3 position (Scheme 1.22).



**Scheme 1.22**

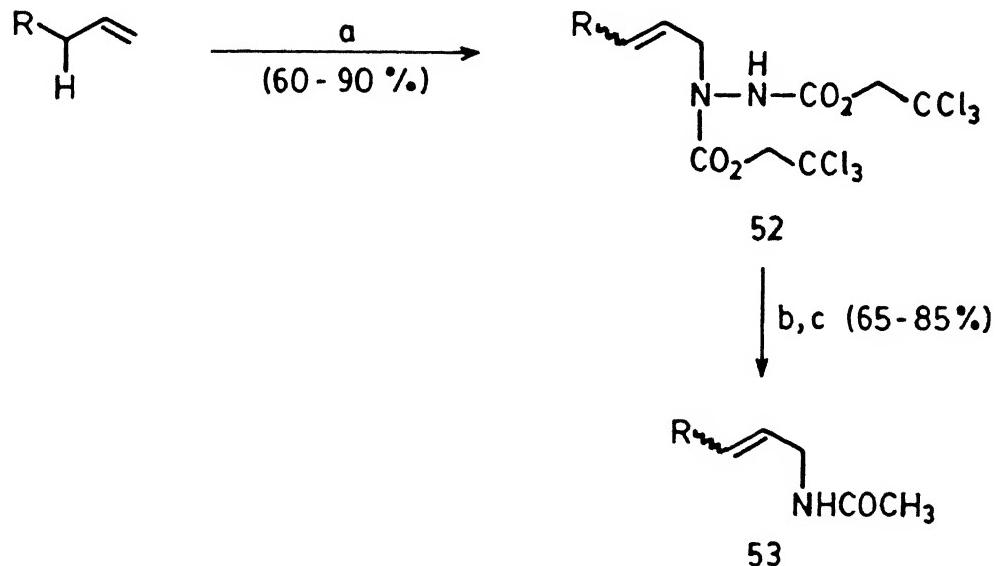
The active catalyst was formed *in situ* by adding Pd(dba)<sub>2</sub> to an appropriate amount of diphos. Deprotection of **50** gave the primary allyl amines **51** (eq. 6).



Synthesis of allyl amides from olefins is an excellent method, since the ready availability of the starting material. Bis(2,2,2-trichloroethyl azodicarboxylate (BTCEAD) is an efficient enophile in the ene reaction with olefins. Leblanc and coworkers<sup>48</sup> synthesized allyl amides from olefins and BTCEAD under mild conditions.

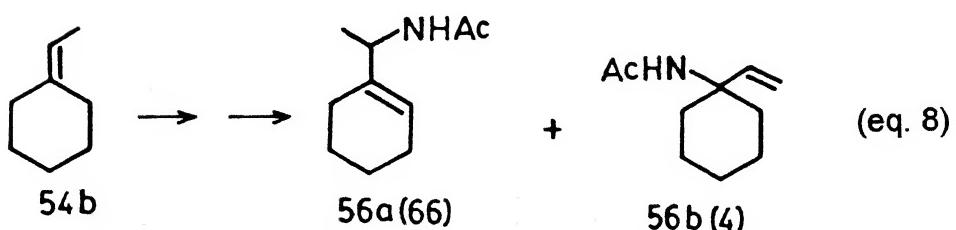
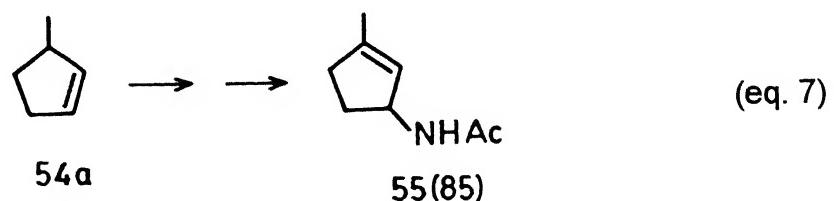
BTCEAD undergoes ene reaction with olefins at 80° C to give the corresponding protected 3-hydrazinoalkenes **52** in excellent yields. The cleavage<sup>49</sup> of the N-N bond of the protected 3-hydrazinoalkenes **52** and the removal of the protecting group with Zn, acetic acid and acetone afforded the allylic acetamides **53** in a single operation (Scheme 1.23).

High regioselectivity was observed in the case of 3-methylcyclopentene **54a** and ethylenecyclohexane **54b** providing predominantly the more substituted olefinic compounds **55** and **56a-b** respectively in high yields (eq. 7,8).



- a)  $\text{Cl}_3\text{CCH}_2\text{O}_2\text{CN} \equiv \text{CO}_2\text{CH}_2\text{CCl}_3$  (BTCEAD)
- b) Zn dust, AcOH then acetone at r.t.
- c)  $\text{Ac}_2\text{O}$ , Py,  $\text{CH}_2\text{Cl}_2$ , r.t., 18h

Scheme 1.23



In view of the importance of allylic amides or amines in organic synthesis, we have undertaken a project to develop a general route to this class of compounds. We have used cobalt(II) complex to achieve these objectives and subsequent part of this chapter deals with our findings.

## 1.2 PRESENT STUDY

In our laboratory it has been observed<sup>50</sup> that cobalt(II) chloride is an efficient catalyst for the acylation of primary and secondary alcohols in the presence of acetic anhydride in acetonitrile at ambient temperature or at 80° C whereas tertiary alcohols showed very little tendency for the acetylation and they were found to afford the corresponding ketone or olefins in low yields. On the other hand, the secondary and tertiary allylic alcohols behaved quite differently under these conditions as they mainly afforded the corresponding allylic amides in moderate to good yields. Thus a variety of secondary alcohols were transformed to the corresponding amides on heating with acetic anhydride in the presence of cobalt(II) chloride in acetonitrile medium (Table 1.1). This treatment also lead to the formation of the corresponding rearranged acetates in low yields. The aromatic allylic alcohol **57** underwent rearrangement to give the corresponding amide whereas the cinnamyl alcohol **58** gave unarranged amide as the main product (Table 1.1, entries 1 and 2). Similarly, the diene alcohol **59** and **60** mainly afforded the unarranged amide **59a** and **60a** respectively along with the trace of the corresponding acetate (Table 1.1, entries 3 and 4). The aliphatic allylic alcohols **61** and **62** yielded a mixture of unarranged and rearranged amides **61a-b** and **62a-b** respectively, however, the rearranged amides were found to be the major product in these reactions (Table 1.1, entries 5 and 6). The acetylenic allylic alcohol **63** was smoothly transformed to the corresponding rearranged amide **63a** exclusively (Table 1.1, entry 7). In all the cases the amides were obtained as a mixture of E- and Z- isomers. Interestingly, the optically pure carveol **64** was converted to the corresponding amide **64a** mainly as a single diastereomer and the optical rotation of the latter indicated it to be a racemic compound. This reaction was also accompanied by the corresponding optically pure acetate (Table 1.1, entry 8) in low yield. In order to examine the compatibility of other

**Table 1.1 : Cobalt (II) Chloride Catalyzed Synthesis of Allylic Amides from Secondary Allylic Alcohols and Nitriles.**

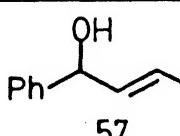
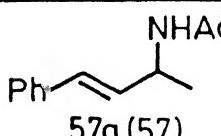
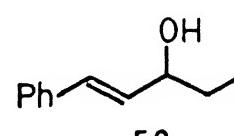
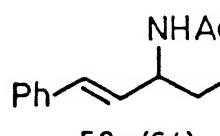
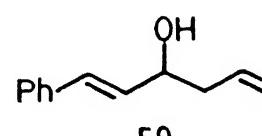
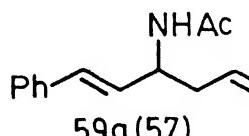
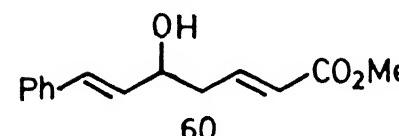
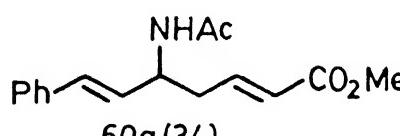
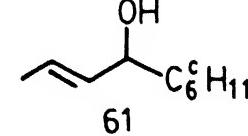
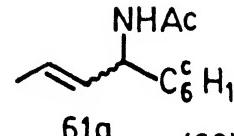
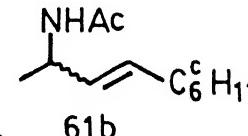
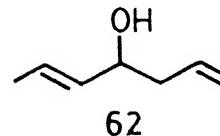
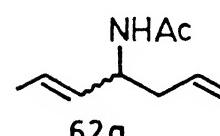
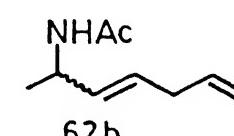
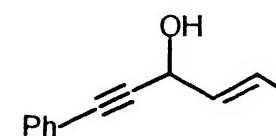
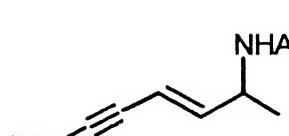
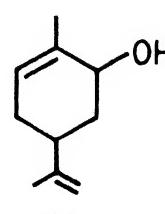
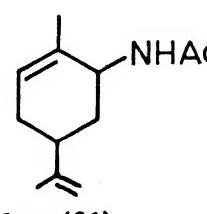
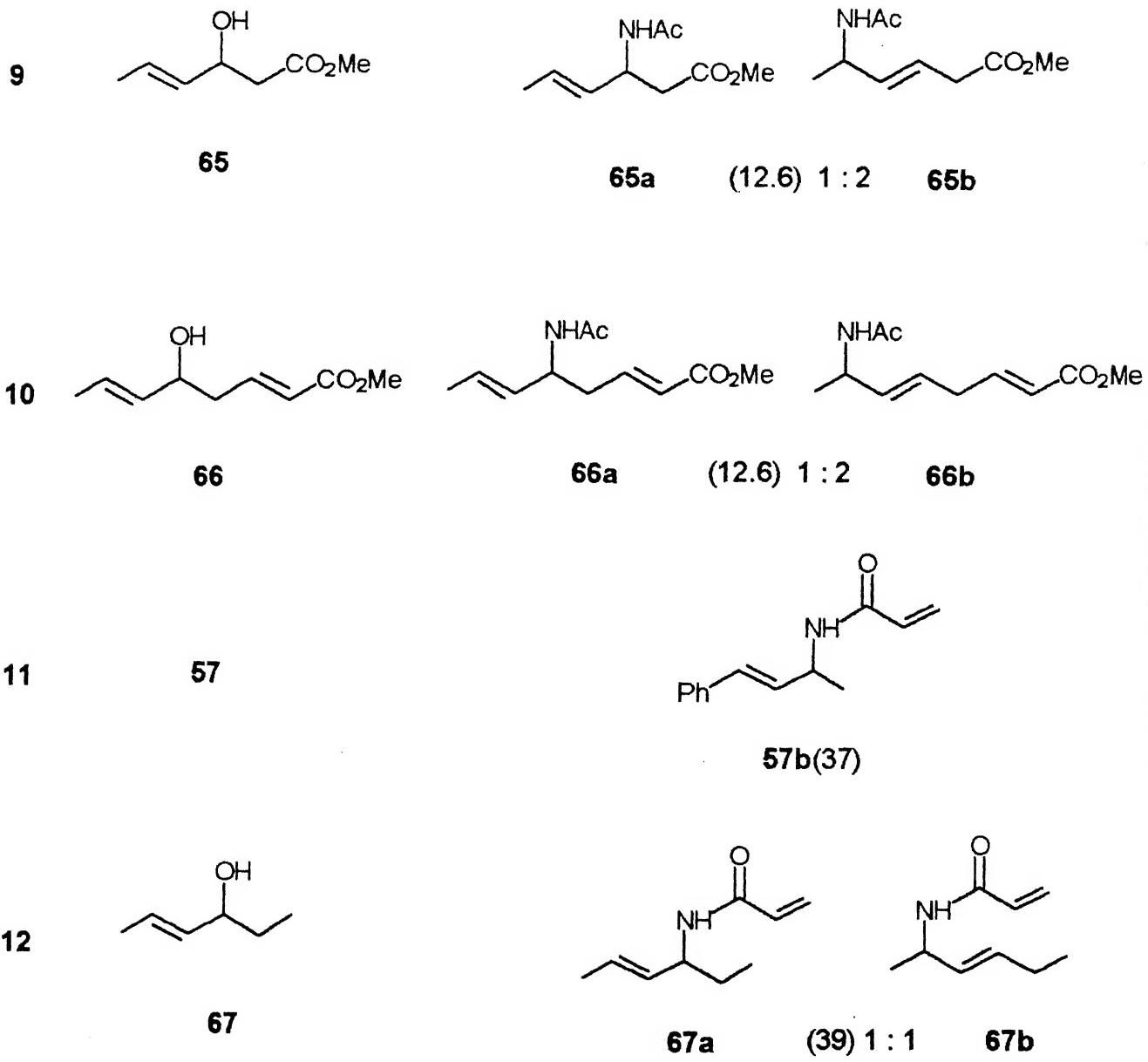
Entry	Alcohol	Products (% Yield)	
1	 57	 57a (57)	
2	 58	 58a (64)	
3	 59	 59a (57)	
4	 60	 60a (34)	
5	 61	 61a (69) 1:1.5	 61b
6	 62	 62a (67) 1:1.5	 62b
7	 63	 63a (54)	
8	 64	 64a (61)	

Table 1.1 continued.....

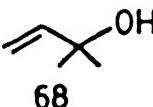
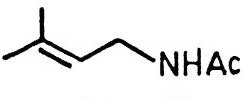
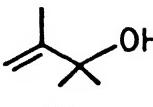
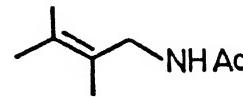
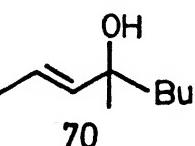
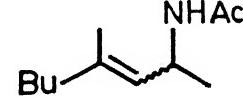
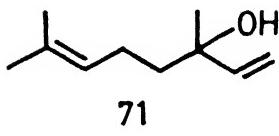
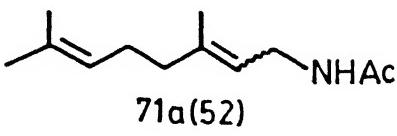
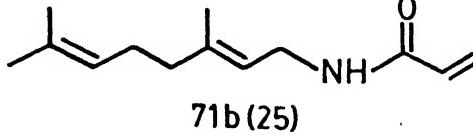
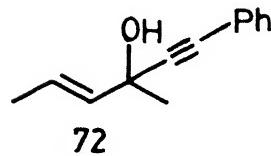
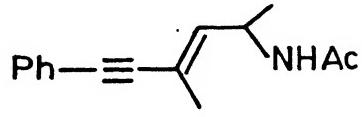
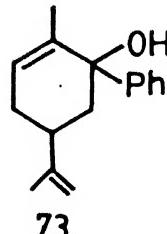
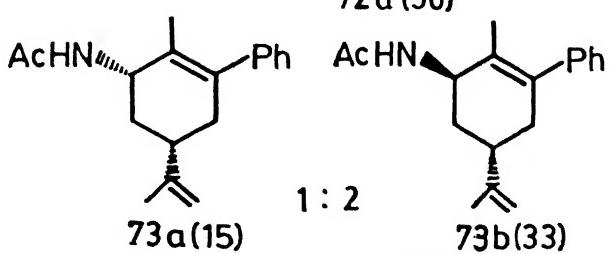
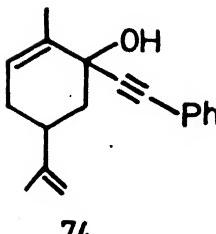
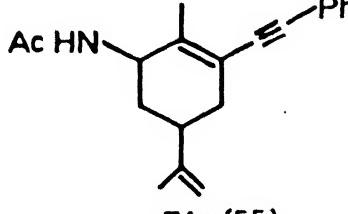


functional groups the reaction was conducted with a variety of allylic alcohols with an ester and olefinic groups. Accordingly, the  $\beta$ -hydroxyesters **65** and **66** were transformed to a mixture of regioisomeric amides **65a-b** and **66a-b** respectively in low yields (Table 1.1, entries 9,10). However, the rearranged amides were found to be the major products under these conditions. It is noteworthy that the rearranged amide is quite useful as an alkene dipeptide isosters which behaves as a transition-state analogues for protease inhibitors. The trans-alkene moiety is a very suitable amide bond surrogate. Moreover, the trans carbon-carbon double bond locks the molecule in a trans geometry whereas the amide bond can also exist in a cis-geometry. Thus our methodology may provide an efficient way to these important mimics for dipeptides<sup>51</sup>. The formation of allylic amides can also be performed by using nitriles other than acetonitrile. Thus alcohols **57** and **67** were converted to the corresponding acrylic amides **57b** and **67a-b** respectively with acrylonitrile in 1,2-dichloroethane in moderate yields (Table 1.1, entries 11 and 12).

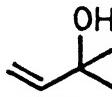
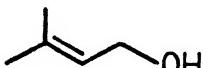
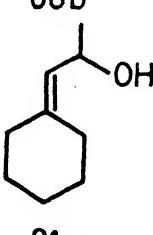
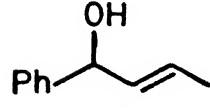
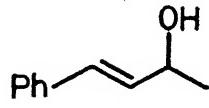
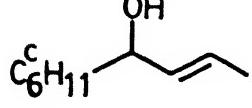
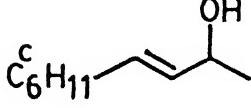
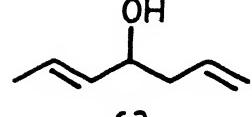
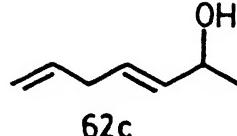
The reaction with tertiary alcohols leads to an exclusive formation of allylically rearranged amides in good yields. The formation of the corresponding acetate is also quite insignificant under these conditions. Thus a variety of tertiary alcohols **68-70** were converted to the corresponding rearranged amides in good yields (Table 1.2, entries 1-3). Linalool **71** was completely transformed to the corresponding rearranged amide **71a** and **71b** with acetonitrile and acrylonitrile respectively in moderate to good yields (Table 1.2, entry 4 and 5). However, the reaction with acrylonitrile also yielded polymeric material. The acetylenic tertiary allylic alcohol **72** gave the rearranged amide **72a** exclusively. The tertiary alcohols **73** and **74** derived from carvone, were converted to a mixture of optically pure diastereomer of the corresponding amides **73a-b** and **74a** respectively (Table 1.2, entries 7 and 8).

It is interesting to note that a catalytic quantity of acetic anhydride also facilitates the formation of the amides over a period of 30-40h. On the other hand the absence of acetic anhydride inhibits the formation of any amide and the allylic alcohols are instead converted to a mixture of regioisomers (Table 1.3). It is noteworthy that the amide formation is also observed in the presence of a catalytic quantity of acetic acid instead of acetic anhydride. The amide formation can also be achieved from the corresponding allyl acetate in the presence of

**Table 1.2 : Cobalt (II) Chloride Catalyzed Synthesis of Allylic Amides from Tertiary Allylic Alcohols and Nitriles.**

Entry	Alcohol	Products (Yield %)
1	 68	 68a (70)
2	 69	 69a (66)
3	 70	 70a (50)
4	 71	 71a (52)
5	71	 71b (25)
6	 72	 72a (56)
7	 73	 73a (15)      1 : 2      73b (33)
8	 74	 74a (55)

**Table 1.3 : Cobalt (II) Chloride Catalyzed Isomerization of Allylic Alcohols.**

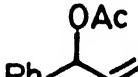
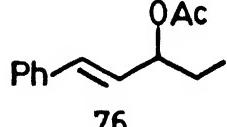
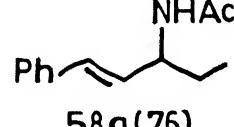
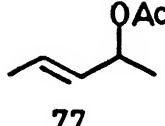
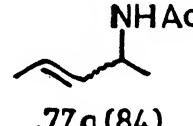
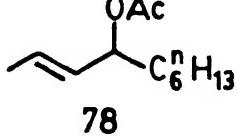
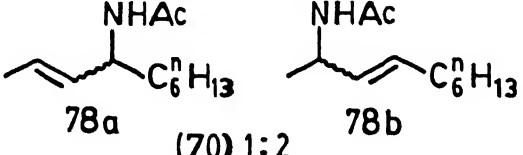
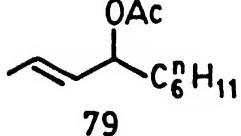
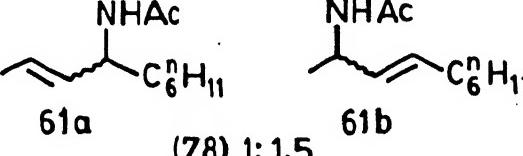
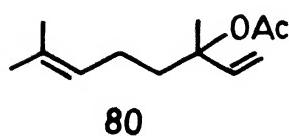
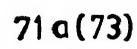
Entry	Alcohol	Product	% of Isomerisation <sup>a,b</sup>
1	 68	 68b	(67)
2	 81	 81a	(85)
3	 57	 57c	(90)
4	 61	 61c	(45)
5	 62	 62c	(40)

a) Obtained from the  $^1\text{H-NMR}$  of the crude reaction mixture.

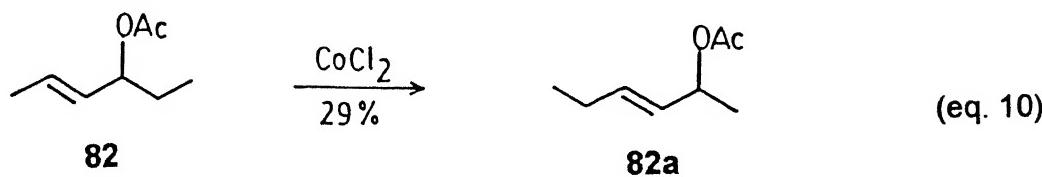
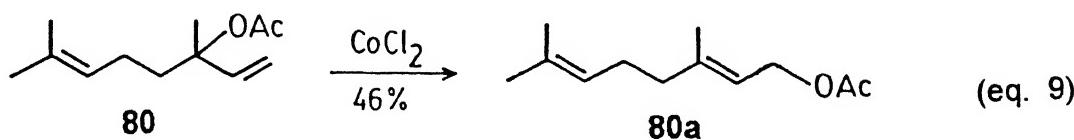
b) Alcohols were heated at  $80^\circ \text{C}$  from 10-12h in the presence of catalytic  $\text{CoCl}_2$

catalytic amount of cobalt(II) chloride and acetic acid (Table 1.4). This protocol provides a relatively higher yields of amide, however, there is no improvement in the regioselectivity as indicated by comparing the results of alcohol 61 (Table 1.1) and acetate 79 (Table 1.4).

**Table 1.4 : Cobalt (II) Chloride Catalyzed Synthesis of Allylic Amides from Secondary and Tertiary Allylic Acetates and Nitriles.**

Entry	Acetate	Products (% Yield)
1	 75	 75a (70)
2	 76	 58a (76)
3	 77	 77a (84)
4	 78	 78a (70) 1:2 78b
5	 79	 61a (78) 1:1.5 61b
6	 80	 71a (73)

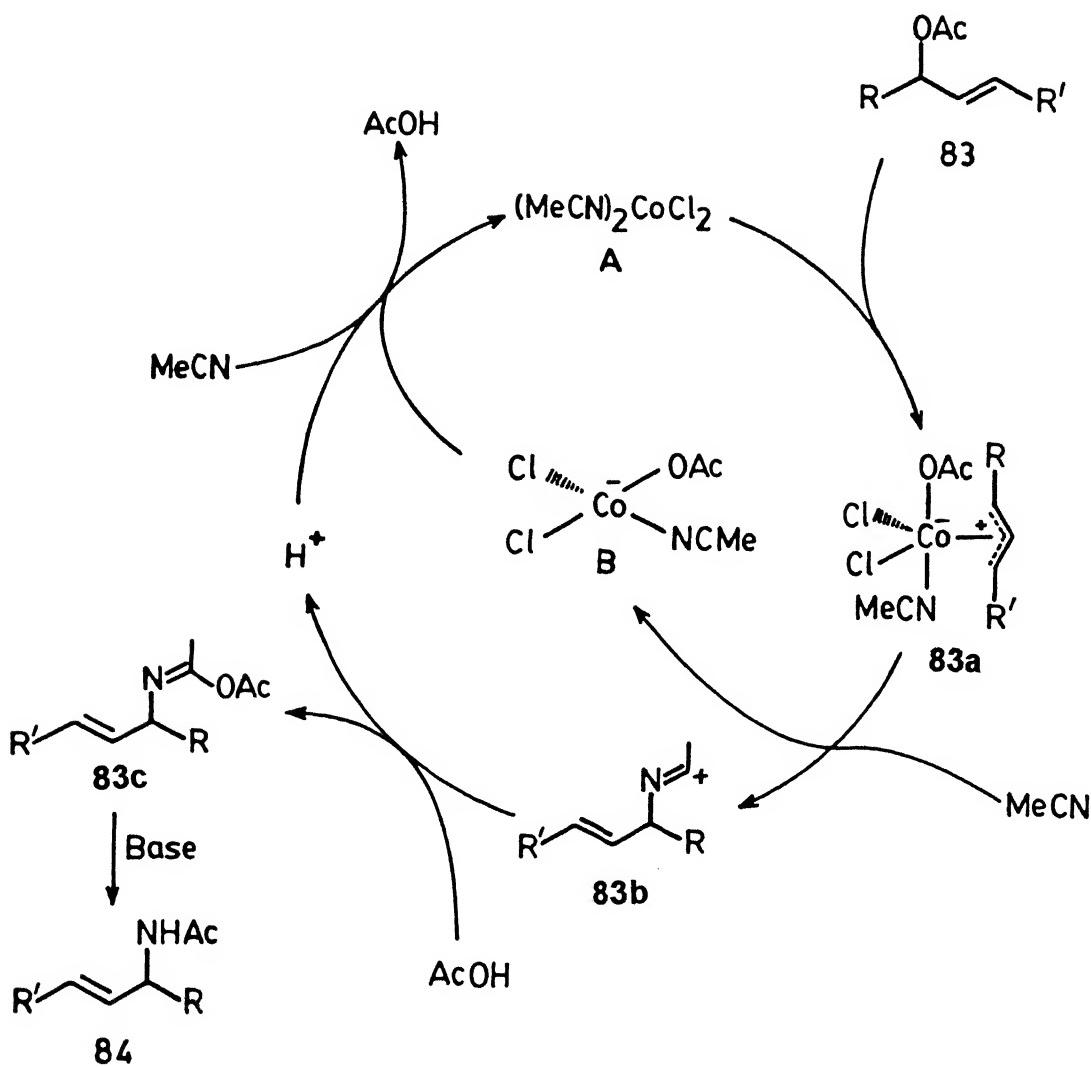
On the other hand, the allyl acetates afforded a mixture of regioisomers in the absence of acetic acid as indicated<sup>52</sup> by the partial rearrangement of **80** and **82** to the corresponding regioisomer **80a** and **82a** respectively (eq. 9 and 10).



## MECHANISM

The absence of amides during the rearrangement of allyl alcohols or acetates clearly reveals that acetic acid is playing a crucial role during the formation of amides. The formation of rearranged amides suggests that the reaction is proceeding via an allyl cation which can be obtained from the corresponding allyl acetate. Thus, initially the allyl alcohols may undergo cobalt(II) chloride catalyzed acylation<sup>50</sup> with acetic anhydride to give the allyl acetate **83** which may afford a cobalt  $\pi$ -allyl complex **83a** on interaction<sup>53</sup> with cobalt(II) (Scheme 1.24). The absence of any products arising out of elimination and the exclusive formation of the rearranged amides from tertiary alcohols indicate it to be a  $\pi$ -allyl complex rather than a solvent<sup>54</sup> stabilised free allyl cation. An intermolecular attack of acetonitrile to the allyl ligand **83a** will provide the cation **83b** which may be attacked by acetic acid to give the imidate ester **83c** and the latter affords the amide **84** during the workup with base (Scheme 1.24). On the other hand, the absence of acetic acid causes the formation of the regioisomer of acetate **83** by reversible elimination-addition of the acetate. Alternatively, the amide formation may be proceeding via allylic acetamide<sup>55</sup> as the formation of the latter in a Pinner reaction<sup>56</sup> and its subsequent [3,3]-sigmatropic rearrangement could be catalyzed by cobalt(II). However, Pinner reaction can

be ruled out in the present case as our preliminary studies have indicated that aqueous acidic

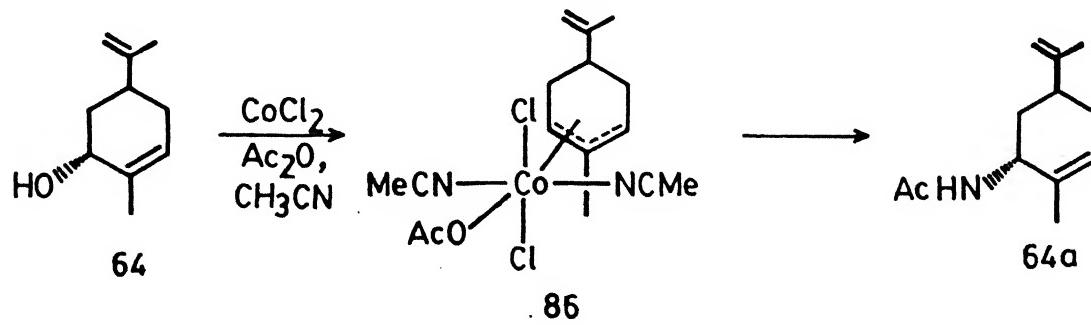


**Scheme 1.24**

workup affords no significant amount of acetate from alcohol in the presence of catalytic cobalt chloride and acetic acid in acetonitrile. The latter observation clearly indicates that imidates are not being formed under these conditions and it is also worth noting that [3,3] sigmatropic rearrangement of imidates will only yield transposed allyl amides rather than a mixture of regioisomers. Moreover, the rearrangement of allylic alcohols or acetates in the absence of acetic

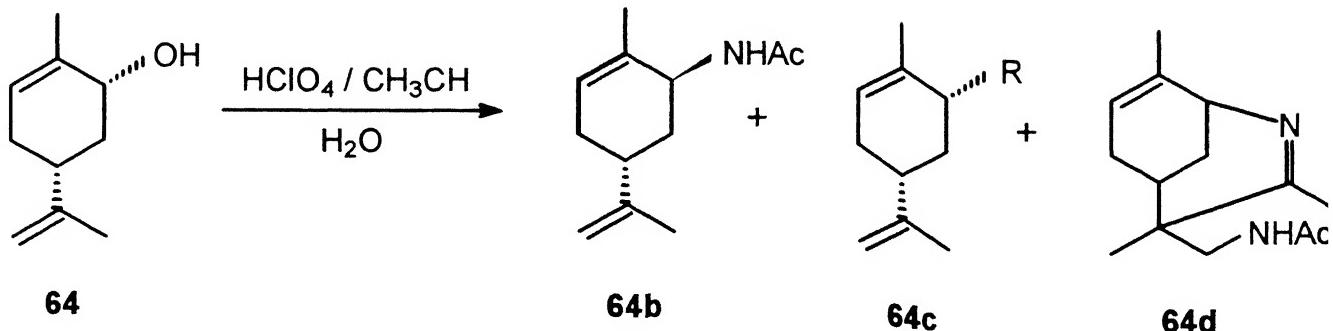
acid also gives an indication that the allyl cation or cobalt  $\pi$ -allyl complex are readily formed under these conditions. The formation of amides from both allyl alcohols and acetates under the aegis of acetic acid and/or acetic anhydride clearly reveals that the reaction is proceeding via allyl acetate. Our recent studies on the cobalt(II) chloride catalyzed allylation of 1,3-dicarbonyl compounds with allyl acetate (see Chapter 3) also strongly suggests the intermediacy of a allyl cation or  $\pi$ -allyl complex in these reactions.

The intermediacy of a cobalt  $\eta^3$ -allyl complex may be further inferred from the stereochemical studies on carveol. Thus the reaction of the optically pure diastereomer of anti alcohol **64** with acetic anhydride in the presence of  $\text{CoCl}_2$  gave racemic mixture of anti amide **64a** (Scheme 1.25).



Scheme 1.25

It is noteworthy that the relative configuration is maintained<sup>54</sup> but the formation of the racemic amide indicates that the reaction is proceeding through the symmetrical  $\eta^3$ -allyl complex **86**, which will undergo nucleophilic attack equally at either end of the allyl group. It is also important to note that these reactions are not proceeding via typical Ritter reaction. This statement is supported by the earlier studies<sup>21</sup> on the carvyl alcohol under typical Ritter conditions which gives rise to the bicyclic product in addition to usual allylic amide (Scheme 1.26). Thus absence of any bicyclic product in our reactions clearly indicates that free allyl cation is not involved in cobalt catalyzed reaction. It is also interesting to note that the cis-carveol mainly led to the cis- amide under these conditions. This observation again supports



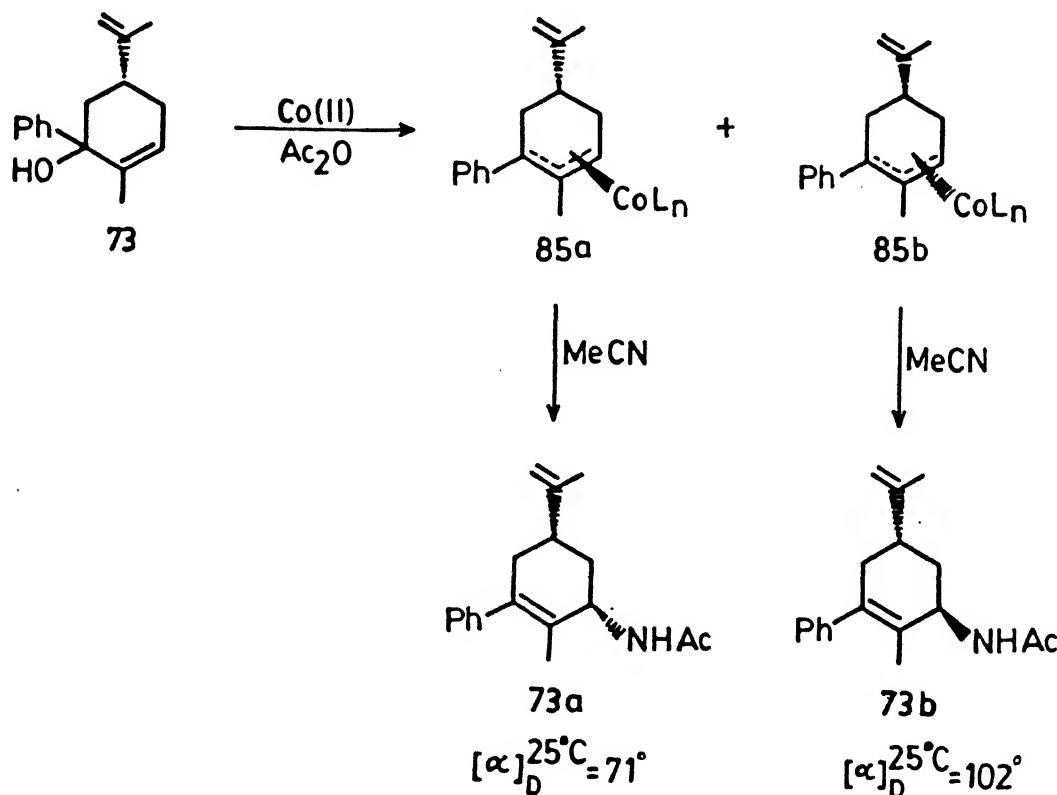
**Scheme 1.26**

the intermediacy of  $\pi$ -allyl complex species in these reactions. A similar studies on the diastereomeric tertiary alcohol 73 also provides a valuable information on the intermediacy of the  $\eta^3$ -allyl complex. Thus one diastereomer of alcohol 73 afforded mainly optically pure syn diastereomer<sup>†</sup> amide 73a whereas the other diastereomer of 73 afforded the anti diastereomer 73b under these conditions (Scheme 1.27). The formation of optically pure diastereomer clearly reveals that the reaction may be proceeding via the anti and syn  $\eta^3$ -allyl complex 85a and 85b which being unsymmetrical, may undergo nucleophilic attack at the less hindered side of the allyl moiety to give the observed regioselectivity.

In view of the above results, the catalytic role of  $\text{CoCl}_2$  and acetic acid may be understood as depicted in Scheme 1.24. The allyl acetate 83 formed by cobalt catalyzed acylation of allyl alcohol with acetic anhydride or acetic acid, will react with cobalt complex A to give a stable cobalt  $\eta^3$ -allyl complex 83a. A nucleophilic attack of the solvent acetonitrile on 83a will lead to the formation of the carbocation 83b and the anionic cobalt complex B. The former may react with acetic acid to afford the imidate ester 83c and the base hydrolysis of the latter will give the allyl amide 84. The proton, generated during the formation of 83c, will react with B to regenerate the cobalt complex A and acetic acid. It is noteworthy that the amide formation is not observed in the absence of acetic acid and this fact strongly supports the

<sup>†</sup>We have assigned the stereochemistry of 73a and 73b based on the  $^1\text{H-NMR}$  pattern where the ( $\text{HC}-\text{N}$ ) proton resonates down field for the anti amide. This is in analogy with the  $^1\text{H-NMR}$  pattern for the amide derived from carveol.

catalytic cycle proposed in Scheme 1.24. The proposed mechanism for this transformation has some resemblance with that of the Ritter reaction<sup>57</sup>. However, regioselectivity in the amide



**Scheme 1.27**

formation from tertiary alcohol appears to be different from what would be expected under classical Ritter conditions. The latter observation also suggests that the free allyl cation is unlikely to be the intermediate in cobalt(II) catalyzed amide formation from allyl alcohol and/or acetate and acetonitrile.

In conclusion, the cobalt(II) chloride catalyzed formation of allylic amides from allylic alcohols and nitriles constitutes a novel methodology which can be of wide applicability in organic synthesis. The reported reaction can be performed under nearly neutral conditions and thus this route provides a viable alternative to Palladium catalyzed synthesis of protected allylic amines which requires a strong hindered base as a source of nitrogen. Some preliminary mechanistic studies on this transformation has indicated the possibility of a cobalt  $\pi$ -allyl complex

as the intermediate and future studies will be undertaken to firmly address this and the related stereo- and regiochemical aspect of this reaction. The application of this methodology to the synthesis of naturally occurring allylic amide will be the ultimate objective of these findings and efforts have already begun to achieve this goal.

## **1.3 EXPERIMENTAL**

### **General Methods and Materials**

IR spectra were recorded on Perkin Elmer 683 Spectrometer. The elemental analysis were carried out on a Coleman automatic C, H and N analyzer.  $^1\text{H-NMR}$  spectra were recorded on Jeol PMX-60, Bruker WP-80 and Bruker WP-200 spectrometer in  $\text{CDCl}_3$  or  $\text{CCl}_4$  using TMS as the internal standard. Multiplicity is indicated using the following abbreviations : s (singlet), br s (broad singlet), br d (broad doublet), d (doublet), dd (doublet of a doublet), t (triplet), dt (doublet of a triplet), q (quartet), qu (quintet), sep (septet), m (multiplet). Optical rotation was taken on JASCO Dip-360 digital polarimeter.

Column chromatography was performed by using ACME silicagel (60-120 mesh) using petroleum ether-ethyl acetate as the eluent. Analytical thin layer chromatography was performed on silicagel (Acme) coated glass plates.

Aldehydes, alkyl halides and acetic anhydride were purchased commercially and purified prior to use. Acetonitrile, THF and ether were purified by standard procedure. Coblat(II) chloride was purchased from LOBA India Ltd., Bombay and dried at  $\sim 120^\circ \text{C}$  for 3-4 h prior to the reaction.

### **General Procedure for the Synthesis of Allylic Alcohols :**

Alcohols were either obtained commercially or prepared either by  $\text{NaBH}_4$  reduction or by Grignard reaction with the corresponding carbonyl compounds. Preparation of some of the representative examples are given below.

#### **1-Phenyl hexa 1,5-diene -3-ol<sup>59</sup> 59**

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  2.35 (t,  $J = 6.5 \text{ Hz}$ , 2H), 2.7 (br s, 1H), 4.3 (q,  $J = 7.0 \text{ Hz}$ , 1H), 4.9-5.3 (m, 2H), 5.5-6.3 (m, 2H), 6.5 (d,  $J = 15 \text{ Hz}$ , 1H), 7.3 (s, 5H).

#### **Methyl 3-hydroxy hex-4-enoate<sup>60</sup> 65**

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.7 (d,  $J = 6.0 \text{ Hz}$ , 3H), 2.3 (d,  $J = 7.5 \text{ Hz}$ , 2H), 3.1 (br s, 1H), 3.6 (s, 3H), 4.0-4.5 (m, 1H), 5.3-5.7 (m, 2H).

IR ( $\text{CCl}_4$ ) :  $\nu_{\text{max}}$  3450, 1730, 1440  $\text{cm}^{-1}$ .

## **General procedure for the preparation of alcohols 63, 72 and 74.**

To a solution of phenyl acetylene (1 mol equiv.) in dry THF, n-butyl lithium (1.2 mol equiv.) was added at  $\sim 20^{\circ}\text{C}$ . Reaction mixture was stirred for 0.5 h. at this temperature and then stirred at room temperature for 0.5 h. A THF solution of aldehyde or ketone (1.2 mol. equiv.) was added dropwise to the reaction mixture at  $0^{\circ}\text{C}$  and stirred for 1 h and then warmed to  $\sim 50^{\circ}\text{C}$ . The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted with ethyl acetate (3x50 mL). The organic layer was washed with saturated  $\text{NH}_4\text{Cl}$  solution and brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent gave a gum which was purified by column chromatography on silica gel.

### **Alcohol 63.**

Yield 73%.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.6 (d,  $J = 7.0\text{ Hz}$ , 3H), 2.6 (br s, 1H), 4.8 (d,  $J = 7.0\text{ Hz}$ , 1H), 5.4-5.8 (m, 2H), 7.1 (s, 5H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  17.49, 63.31, 85.81, 88.58, 122.57, 128.24, 128.42, 128.84, 130.23, 131.69, 149.63.

IR (thin film) :  $\nu_{\text{max}}$  3380, 3080, 2200  $\text{cm}^{-1}$ .

### **Alcohol 72.**

Yield 75%.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.4 (s, 3H), 1.7 (d,  $J = 7.0\text{ Hz}$ , 3H), 2.2 (br s, 1H), 5.5-6.1 (m, 2H), 7.1 (s, 5H).

IR (thin film) :  $\nu_{\text{max}}$  3380, 3080, 2200  $\text{cm}^{-1}$ .

### **Alcohol 74.**

Yield 70%.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.7 (s, 6H), 1.8-2.1 (m, 5H), 2.3 (br s, 1H), 4.6 (s, 2H), 5.3 (m, 1H), 7.0 (s, 5H).

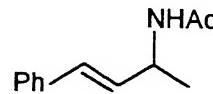
IR (thin film) :  $\nu_{\text{max}}$  3400, 3060, 2200  $\text{cm}^{-1}$ .

## **General Procedure for the Synthesis of Allylic Amides**

Allylic alcohol (10 mmol) and acetic anhydride (12 mmol) were added to a solution of

cobalt(II) chloride (5 mol %) in dry acetonitrile (100 mL). The reaction mixture was heated to 80° C for 15-20h and the progress of the reaction was monitored by TLC. Removal of the solvent yielded a residue which was taken into ethyl acetate (50 mL) and the organic layer was washed successively with saturated sodium bicarbonate solution (5x20 mL), water (3x20 mL) and brine (1x30 mL). Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent yielded a residue which was subjected to column chromatography to afford allylic amides in good yields.

**3-Acetamido 1-phenyl but-1-ene 57a.**



Reaction of **57** (1.27g, 8.58 mmol), acetic anhydride (1.05g, 10.3 mmol) and  $\text{CoCl}_2$  (~50 mg) in acetonitrile (100 mL) at 80° C for 10h gave **57a** (0.6g, 37%); m.p. 91°C.

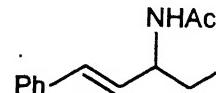
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  1.2 (d,  $J = 7.5$  Hz, 3H), 1.85 (s, 3H), 4.3-4.7 (m, 1H), 5.9-6.1 (m, 1H), 6.25 (d,  $J = 16$  Hz, 1H), 7.0 (s, 5H).

IR (KBr) :  $\nu_{\text{max}}$  3280, 3080, 1630  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{15}\text{NO}$  : C, 76.19; H, 7.93.

Found : C, 76.26; H 7.97.

**3-Acetamido 1-phenyl pent-1-ene 58a.**



The reaction was performed as described above with **58** (0.86 g, 5.3 mmol),  $\text{CoCl}_2$  (~50 mg) in acetonitrile (100 mL) and acetic anhydride (0.65g, 6.36 mmol). Purification by column chromatography ( $\text{SiO}_2$ ) afforded **58a** (0.69g, 64%); m.p. 115° C.

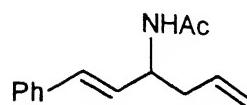
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  0.9 (t,  $J = 7.0$  Hz, 3H), 1.5 (m, 2H), 1.9 (s, 3H), 4.4 (m, 1H), 5.9-6.1 (m, 1H), 6.3 (d,  $J = 16$  Hz, 1H), 7.1 (s, 5H).

IR (KBr) :  $\nu_{\text{max}}$  3300, 3080, 1630  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{13}\text{H}_{17}\text{NO}$  : C, 76.86; H, 8.37.

Found: C, 76.95; H, 8.42.

**3-Acetamido 1-phenyl hexa-1,5-diene 59a.**



Reaction of **59** (1.0g, 5.7 mmol) with  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acetonitrile (100 mL) and acetic anhydride (0.81g, 7.98 mmol) by the above described procedure followed by column chromatography on silica gel afforded **59a** (0.70g, 57%); m.p.  $95^\circ \text{C}$ .

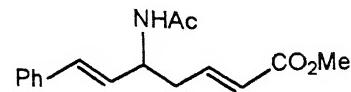
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.85 (s, 3H), 2.25 (t,  $J = 7.5$  Hz, 2H), 4.5 (m, 1H), 4.7-5.1 (m, 2H), 5.3-6.1 (m, 2H), 6.3 (d,  $J = 16$  Hz, 1H), 6.5 (br d, 1H), 7.1 (s, 5H).

IR ( $\text{CCl}_4$ ) :  $\nu_{\max}$  3300, 3080, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}$  : C, 78.15; H, 7.90.

Found: C, 78.25; H, 7.94.

**Methyl 5-acetamido 7-Phenyl hepta-2,6-dienoate 60a.**



Prepared from **60** (0.47g, 2.02 mmol) by treatment with acetic anhydride (0.25 gms, 2.43 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in acetonitrile (100 mL) at  $80^\circ \text{C}$  for 40h. Column chromatography (4:1 ethyl acetate, petroleum ether) afforded **60a** (0.27g, 24.4%).

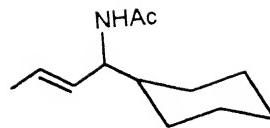
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.9 (s, 3H), 2.1-2.6 (m, 2H), 3.5 (s, 3H), 4.4 (m, 1H), 5.5-6.3 (m, 4H), 6.8-7.2 (m, 6H).

IR (Thin film) :  $\nu_{\max}$  3280, 3040, 1720, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_3$  : C, 70.35; H, 6.96.

Found: C, 70.42; H, 7.03.

**4-Acetamido 4-cyclohexyl but-2-ene 61a.**

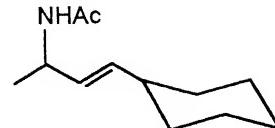


This reaction was performed as described above with **61** (0.6g, 3.9 mmol),  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acetonitrile (100 mL) and acetic anhydride (0.60g, 5.85 mmol). Purification by chromatography ( $\text{SiO}_2$ ) afforded **61a** 26% (0.20g).

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.2-1.6 (m, 11H), 1.65 (d,  $J = 5.8$  Hz, 3H), 1.85 (s, 3H), 3.8-4.25 (m, 1H), 5.0-5.5 (m, 2H), 7.2 (br d, 1H).

IR (Thin film) :  $\nu_{\text{max}}$  3310, 3090, 1650  $\text{cm}^{-1}$ .

**3-Acetamido 1-cyclohexyl but-1-ene 61b.**



This isomer was separated from the reaction mixture as described for **61a** in 43% (0.33g).

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.1 (d,  $J = 7.0$  Hz, 3H), 1.3-1.7 (m, 11H), 1.8 (s, 3H), 4.3 (m, 1H), 5.3 (m, 2H), 7.2 (br d, 1H).

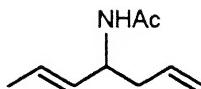
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  20.85, 23.44, 26.02, 26.14, 32.89, 40.30, 46.44, 53.58, 70.36, 128.57, 136.63, 169.33.

IR ( $\text{CCl}_4$ ) :  $\nu_{\text{max}}$  3310, 3090, 1650  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{21}\text{NO}$  : C, 73.86; H, 10.76.

Found: C, 73.92; H, 10.81.

**4-Acetamido hept-1,5-diene 62a.**



Compound **62** (1.0g, 8.9 mmol), acetic anhydride (1.36g, 13.35 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50

mg) were heated to 80° C in acetonitrile (100 mL) to afford **62a** (27.2%, 0.37g).

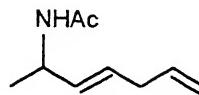
<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.6 (d, J = 6.0 Hz, 3H), 1.8 (s, 3H), 2.15 (t, J = 7.0 Hz, 2H), 4.3 (m, 1H), 4.6-5.7 (m, 5H), 7.15 (br d, 1H).

IR (KBr) : ν<sub>max</sub> 3300, 3080, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>15</sub>NO : C, 70.58; H, 9.80.

Found: C, 70.67; H, 9.87.

**6-Acetamido hepta-1,4-diene 62b.**



This isomer was separated from the reaction mixture as described for **62a** in 40% (0.55g) yield.

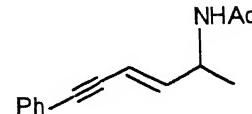
<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.1 (d, J = 8.0 Hz, 3H), 1.8 (s, 3H), 2.6 (m, 2H), 4.3 (m, 1H), 4.6-5.7 (m, 5H), 7.15 (br d, 1H)

IR (KBr) : ν<sub>max</sub> 3310, 3080, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>15</sub>NO : C, 70.60; H, 9.80.

Found: C, 70.69; H, 9.85.

**5-Acetamido 1-phenyl hex-3-ene-1-yne 63a.**



Compound **63** (0.50g, 3.49 mmol), acetic anhydride (0.53g, 5.2 mmol) and CoCl<sub>2</sub> (~30 mg) in acetonitrile (100 mL) were heated to 80° C. column chromatography (SiO<sub>2</sub>, 2:3 ethyl acetate, petroleum ether) of the crude yielded **63a** (0.40g, 54%); m.p. 104-105° C.

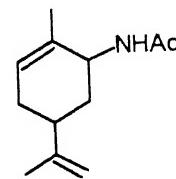
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 1.3 (d, J = 7.5 Hz, 3H), 2.0 (s, 3H), 4.6-4.8 (m, 1H), 5.5-5.95 (m, 1H), 6.1-6.3 (dd, J = 16.0 and 6.0 Hz, 1H), 7.4 (m, 6H).

IR (KBr) : ν<sub>max</sub> 3280, 3080, 1630 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>NO : C, 78.89; H, 7.04.

Found: C, 78.96; H, 7.11.

**3-Acetamido-5-isopropenyl-2-methylcyclohex-1-ene 64a.**



Prepared as described above by reacting carveol **64** (0.83g, 5.4 mmol), acetic anhydride (0.66g, 6.4 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in acetonitrile (100 mL) at  $80^\circ\text{C}$  for 12h. Column chromatography of crude residue (1:3 EtOAc, petroleum ether) afforded **64a** (0.64g, 61%); m.p.  $56\text{-}58^\circ\text{C}$ .

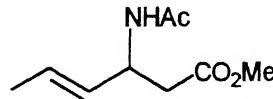
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.6 (s, 6H), 1.85 (m, 8H), 4.2 (m, 1H), 4.5 (s, 2H), 5.4 (m, 1H), 7.3 (br d, 1H)

IR (KBr) :  $\nu_{\text{max}}$  3280, 3080, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{19}\text{NO}$  : C, 74.63; H, 9.84.

Found: C, 74.72; H, 9.87.

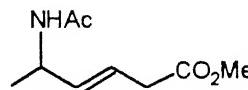
**Methyl 3-acetamido hexa-4-enoate 65a.**



Prepared as described above by the reaction of **65** (0.74g, 5.14 mmol), acetic anhydride (1.05g, 10.3 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in acetonitrile (100 mL) at  $80^\circ\text{C}$  for 20h. Column chromatography (4:1 ethyl acetate, petroleum ether) of the crude residue afforded **65a** (0.04g, 4%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  1.6 (d,  $J = 5.0$  Hz, 3H), 1.8 (s, 3H), 2.5 (d,  $J = 6.25$  Hz, 2H), 3.68 (s, 3H), 4.5-4.87 (m, 1H), 5.4-5.8 (m, 2H), 6.15 (br d, 1H).

IR (Thin film) :  $\nu_{\text{max}}$  3280, 3070, 1730, 1640  $\text{cm}^{-1}$

**Methyl 5-acetamido hex-3-enoate 65b**

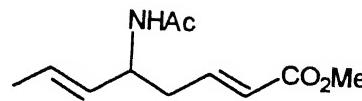
This isomer was separated from the reaction mixture as described for **65a** in 8.4% (0.08g) yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 1.1 (d, J = 6.25 Hz, 3H), 1.9 (s, 3H), 3.0 (d, J = 5.0 Hz, 2H), 3.65 (s, 3H), 4.3-4.65 (m, 1H), 5.3-5.65 (m, 2H), 5.75 (br d, 1H).

IR (Thin film) : ν<sub>max</sub> 3280, 3070, 1730, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub> : C, 58.40; H, 8.10.

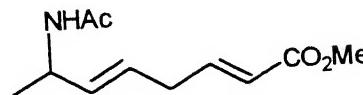
Found: C, 58.52; H, 8.16.

**Methyl 5-acetamido octa-2,6-dienoate 66a.**

Reaction was performed as described above with **66** (1.53g, 9 mmol), acetic anhydride (0.9g, 9 mmol) and CoCl<sub>2</sub> (~50 mg) in acetonitrile (100 mL) at 80° C for 30h. Chromatography of the crude product yielded **66a** (0.08g, 4.2%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.65 (d, J = 6.25 Hz, 3H), 1.9 (m, 5H), 3.55 (s, 3H), 4.3 (m, 1H), 4.8-6.1 (m, 4H), 7.1 (br d, 1H).

IR (Thin film) : ν<sub>max</sub> 3360, 3080, 1720, 1640 cm<sup>-1</sup>

**Methyl 7-acetamido octa-2,5-dienoate 66b.**

This isomer was separated from the reaction mixture as described for **66a** (0.16g, 8.4%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.2 (d, J = 6.25 Hz, 3H), 1.8 (m, 2H), 1.9 (s, 3H), 3.6 (s, 3H), 4.4 (m,

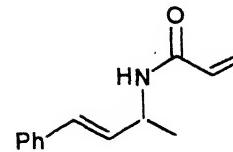
1H), 5.1-5.9 (m, 3H), 6.4-7.0 (m, 2H).

IR (Thin film) :  $\nu_{\text{max}}$  3320, 3080, 1720, 1650  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{17}\text{NO}_3$  : C, 62.58; H, 8.05.

Found: C, 62.71; H, 8.12.

**3-(Prop-1'-enamido) 1-phenyl but-1-ene 57b.**



Compound **57** (1.1g, 7.5 mmol), acetic anhydride (0.38g, 3.75 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) were heated in acrylonitrile at  $70^\circ \text{C}$  for 10h. Chromatography of the crude product afforded **57b** (0.55g, 37%); m.p.  $108^\circ \text{C}$ .

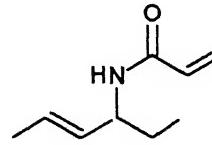
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  1.3 (d,  $J = 7.5 \text{ Hz}$ , 3H), 4.6-5.05 (m, 1H), 5.7 (dd,  $J = 10.0$  and  $3.75 \text{ Hz}$ , 1H), 5.85-6.4 (m, 3H), 6.6 (d,  $J = 16 \text{ Hz}$ , 1H), 7.05-7.6 (m, 6H).

IR (KBr) :  $\nu_{\text{max}}$  3280, 3060, 1645  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}$  : C, 77.62; H, 7.46.

Found: C, 77.72; H, 7.52.

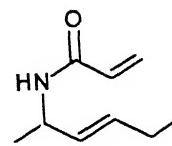
**4-(Prop-1'-enamido)-hex-2-ene 67a.**



Prepared as described above by the reaction of **67** (0.95g, 9.5 mmol), acetic anhydride (0.48g, 4.75 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acrylonitrile (20 mL) at  $80^\circ \text{C}$  for 10h. Column chromatography (2:3 ethyl acetate, petroleum ether) afforded **67a** (0.26g, 18%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  0.9 (t,  $J = 7.5 \text{ Hz}$ , 3H), 1.3-1.5 (m, 2H), 1.6 (d,  $J = 6.25 \text{ Hz}$ , 3H), 4.05-4.7 (m, 1H), 5.3-5.7 (m, 3H), 6.1-6.2 (m, 2H).

IR ( $\text{CCl}_4$ ) :  $\nu_{\text{max}}$  3280, 3060, 1640  $\text{cm}^{-1}$ .

**2-(Prop-1'-enamido)-hex-4-ene 67b.**

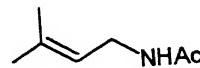
This isomer was separated from the reaction mixture as described for **67a** in 21% (0.30g) yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 0.85 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.7-2.1 (m, 2H), 4.05-4.7 (m, 1H), 5.3-5.7 (m, 3H), 6.1-6.2 (m, 2H).

IR (thin film) : ν<sub>max</sub> 3300, 3060, 1650 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>15</sub>NO : C, 70.59; H, 9.80.

Found: C, 70.69; H, 9.92.

**4-Acetamido 2-methyl but-2-ene 68a.**

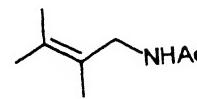
This compound was prepared from **68** (0.86g, 10 mmol), acetic anhydride (1.2g, 12 mmol) and CoCl<sub>2</sub> (~50 mg) in acetonitrile (100 ML). The crude product was purified by column chromatography (SiO<sub>2</sub>) to afford **68a** (0.62g, 70%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) δ 1.7 (s, 6H), 1.9 (s, 3H), 3.7(t, J = 7.0 Hz, 2H), 5.1 (t, J = 7.0 Hz, 1H), 7.1 (br d, 1H).

IR (thin film) : ν<sub>max</sub> 3300, 3080, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>7</sub>H<sub>13</sub>NO : C, 66.16; H, 10.23.

Found: C, 66.27; H, 10.29.

**4-Acetamido 2,3-dimethyl but-2-ene 69a.**

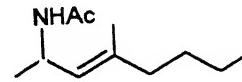
Reaction was performed as described above with crude alcohol **69** (0.6g, 5.94 mmol), acetic anhydride (0.73g, 7.13 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in acetonitrile (100 mL) at  $80^\circ \text{C}$  for 15h to afford **69a** (0.55g, 66%).

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  1.7 (s, 9H), 1.9 (s, 3H), 3.7 (d,  $J = 9$  Hz, 2H), 7.2 (br d, 1H).

IR (Thin film) :  $\nu_{\text{max}}$  3300, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_8\text{H}_{15}\text{NO}$  : C, 68.10; H, 10.63.

Found: C, 68.21; H, 10.69.

**4-Acetamido 4-methyl oct-2-ene 70a**

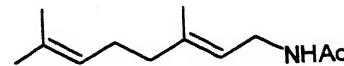
Alcohol **70** (0.70g, 4.93 mmol) acetic anhydride (0.75g, 7.4 mmol)  $\text{CoCl}_2$  ( $\sim$ 30 mg) in acetonitrile (100 mL) were heated to  $80^\circ \text{C}$  for 15h to afford **70a** (0.45g, 50%).

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  0.8-1.0 (m, 3H), 1.1-1.5 (m, 7H), 1.8 (s, 3H), 1.9 (s, 3H), 2.1 (m, 2H), 3.9-4.5 (m, 1H), 5.3-5.7 (m, 1H), 7.2 (br d, 1H).

IR (Thin film) :  $\nu_{\text{max}}$  3280, 3080, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{21}\text{NO}$  : C, 72.13; H, 11.47.

Found: C, 72.17; H, 11.52.

**8-Acetamido 2,6-dimethyl oct-2,6-diene 71a**

Following the same procedure as above, linalool, **71** (1.2g, 7.7 mmol), acetic anhydride

(0.94g, 9.24 mmol), CoCl<sub>2</sub> (~50 mg) in acetonitrile (100 mL) were heated at 80° C for 20h to afford **71a** (0.78g, 52%).

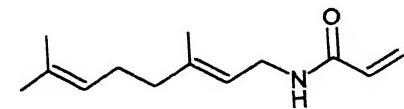
<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.6 (s, 3H), 1.65 (s, 6H), 1.8 (s, 3H), 1.9 (m, 4H), 3.6 (m, 2H), 4.9 (m, 2H), 5.9 (m, 1H).

IR (Thin film) : ν<sub>max</sub> 3320, 3090, 1650 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>21</sub>NO : C, 73.86; H, 10.76.

Found: C, 73.99; H, 10.82.

**8-(Prop-1'-enamido)-2,6-dimethyl-oct-2,6-diene 71b.**



Linalool, **71** (1.04g, 6.77 mmol), acetic anhydride (0.41g, 4.06 mmol) and CoCl<sub>2</sub> (~50 mg) in acrylonitrile (20 mL) and 1,2-dichloroethane (30 mL) were subjected to the reaction conditions as described above for 10h to afford **71b** (0.21g, 15%); m.p. 104-106° C.

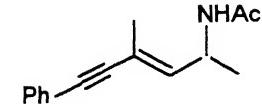
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 1.6 (s, 3H), 1.65 (s, 6H), 1.75-2.35 (m, 4H), 3.9 (m, 2H), 4.9-5.35 (m, 2H), 5.45-6.3 (m, 3H), 7.2 (m, 1H).

IR(KBr) : ν<sub>max</sub> 3260, 3060, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>13</sub>H<sub>21</sub>NO : C, 75.38; H, 10.14.

Found: C, 75.52; H, 10.25.

**5-Acetamido 3,5-dimethyl 1-phenyl pent-3-ene-1-yne 72a.**



This compound was prepared as described above by the reaction of **72** (0.65g, 3.49 mmol), acetic anhydride (0.64g, 6.28 mmol) and CoCl<sub>2</sub> (~30 mg) in acetonitrile (100 mL) at 80° C for 10h followed by column chromatography (SiO<sub>2</sub>) in 56% (0.44g) yield.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 1.15 (d, J = 7.5 Hz, 3H), 1.8 (s, 3H), 1.85 (s, 3H), 4.7 (m, 1H), 5.5 (br d, 1H), 7.1 (m, 6H).

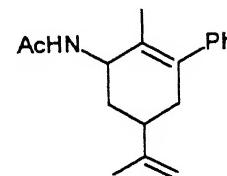
<sup>13</sup>C NMR (CDCl<sub>3</sub>) :  $\delta$  21.10, 23.16, 46.05, 119.68, 123.11, 128.30, 129.93, 130.94, 131.56, 138.29, 141.85, 169.45.

IR (KBr) :  $\nu_{\text{max}}$  3300, 3060, 2100, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>17</sub>NO : C, 79.31; H, 7.58.

Found: C, 79.37; H, 7.63.

**3-Acetamido-5-isopropenyl-2-methyl-1-phenyl cyclohex-1-ene 73a and 73b.**



This compound was prepared as described above by the reaction of alcohol **73** (1.64g, 7.19 mmol), acetic anhydride (0.88g, 8.63 mmol) and CoCl<sub>2</sub> (~50 mg) in acetonitrile (100 mL) at 80° C for 12h in 48% (0.93g) yield as a mixture of diastereomers. m.p 129° C.

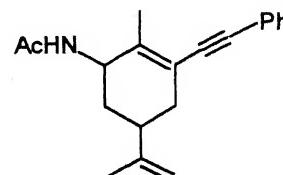
<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  1.65 (s, 3H), 1.78 (s, 3H), 1.95 (m, 3H), 2.05 (s, 3H), 2.28 (m, 3H), 4.45-4.75 (m, 1H), 4.8 (s, 2H), 5.6 (br d, 1H), 7.3 (s, 5H).

IR (KBr) :  $\nu_{\text{max}}$  3300, 3080, 1630 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>18</sub>H<sub>23</sub>NO : C, 80.31; H, 8.54.

Found : C, 80.39; H, 8.58.

**3-Acetamido-5-isopropenyl methyl 1-(2'-phenylethyynyl)cyclohex-1-ene 74a.**



Alcohol **74** (0.75g, 2.98 mmol), acetic anhydride (0.36g, 3.57 mmol) and cobalt chloride (~30 mg) were heated in acetonitrile (100 mL) at 80° C for 10 hrs. Column chromatography of the crude product afforded **74a** (0.48g, 55%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) :  $\delta$  1.7 (s, 6H), 1.85 (s, 3H), 2.0-2.6 (m, 5H), 4.1-4.5 (m, 1H), 4.6 (s, 2H), 7.15 (m, 6H).

IR (KBr) :  $\nu_{\text{max}}$  3300, 3080, 2200, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>20</sub>H<sub>23</sub>NO : C, 81.92; H, 7.84.

Found: C, 82.01; H, 7.91.

**3-Acetamido 1-phenyl prop-1-ene 75a.**



The acetate **75** (1.76g, 10 mmol), acetic acid ( $\sim$ 100 mg), CoCl<sub>2</sub> ( $\sim$ 50 mg) in dry acetonitrile (100 mL) were heated at 85° C for 30h. Usual workup followed by column chromatography afforded **75a** (1.2g, 70%).

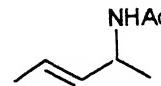
<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  1.85 (s, 3H), 3.9 (m, 2H), 6.0-6.5 (m, 1H), 6.65 (d, J = 16 Hz, 1H), 7.1 (s, 5H), 7.2 (m, 1H).

IR (CCl<sub>4</sub>) :  $\nu_{\text{max}}$  3280, 3080, 1630 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>11</sub>H<sub>12</sub>NO : C, 75.44; H, 7.42.

Found: C, 75.59; H, 7.51.

**4-Acetamido pent-2-ene 77a.**

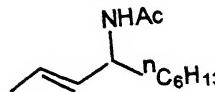


The reaction was performed as described above with allyl acetate **77** (1.14g, 8.9 mmol), acetic acid ( $\sim$ 100 mg) and CoCl<sub>2</sub> ( $\sim$ 50 mg) in dry acetonitrile (100 mL). Usual workup followed by column chromatography afforded **77a** (0.9g, 84%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  1.2 (d, J = 7.5 Hz, 3H), 1.6 (d, J = 6.0 Hz, 3H), 1.8 (s, 3H), 4.0-4.5 (m, 1H), 5.2-5.3 (m, 2H), 7.15 (br d, 1H).

IR (CCl<sub>4</sub>) :  $\nu_{\text{max}}$  3300, 3050, 1630 cm<sup>-1</sup>.

**4-Acetamido dec-2-ene 78a.**



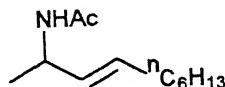
The reaction was performed with **78** (0.99g, 5 mmol), acetic acid ( $\sim$ 100 mg) and CoCl<sub>2</sub>

(~50 mg) as described above. Usual workup followed by column chromatography of the crude product afforded **78a** (0.22g, 23%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 0.9 (m, 3H), 1.0-1.3 (m, 10H), 1.6 (d, J = 7.0 Hz, 3H), 1.8 (s, 3H), 4.2 (m, 1H), 5.4 (m, 2H), 6.1 (br d, 1H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 3300, 3050, 1630 cm<sup>-1</sup>.

**2-Acetamido dec-3-ene 78b.**



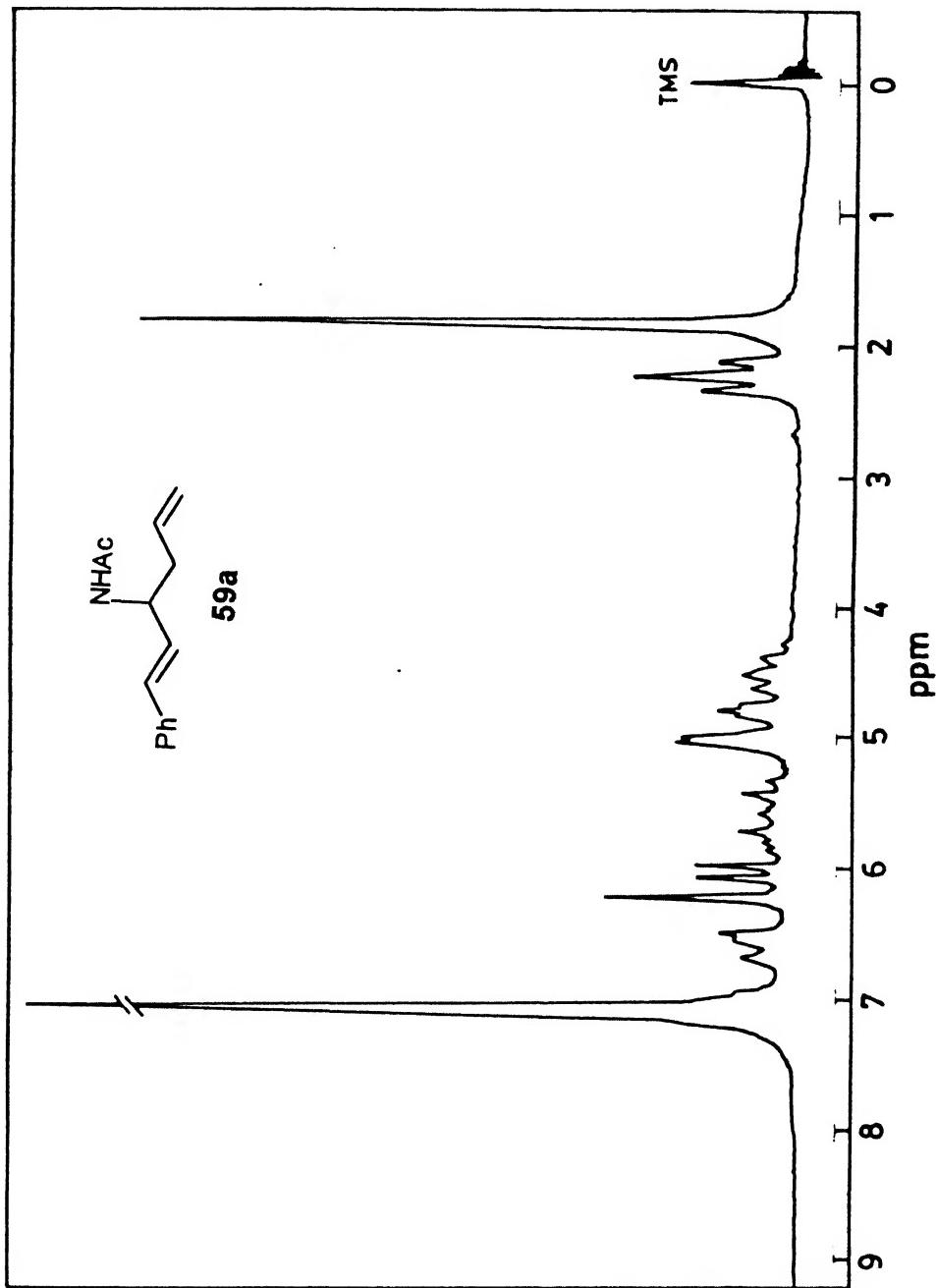
This compound was separated from the reaction mixture as described for **78a** in 47% (0.46g) yield.

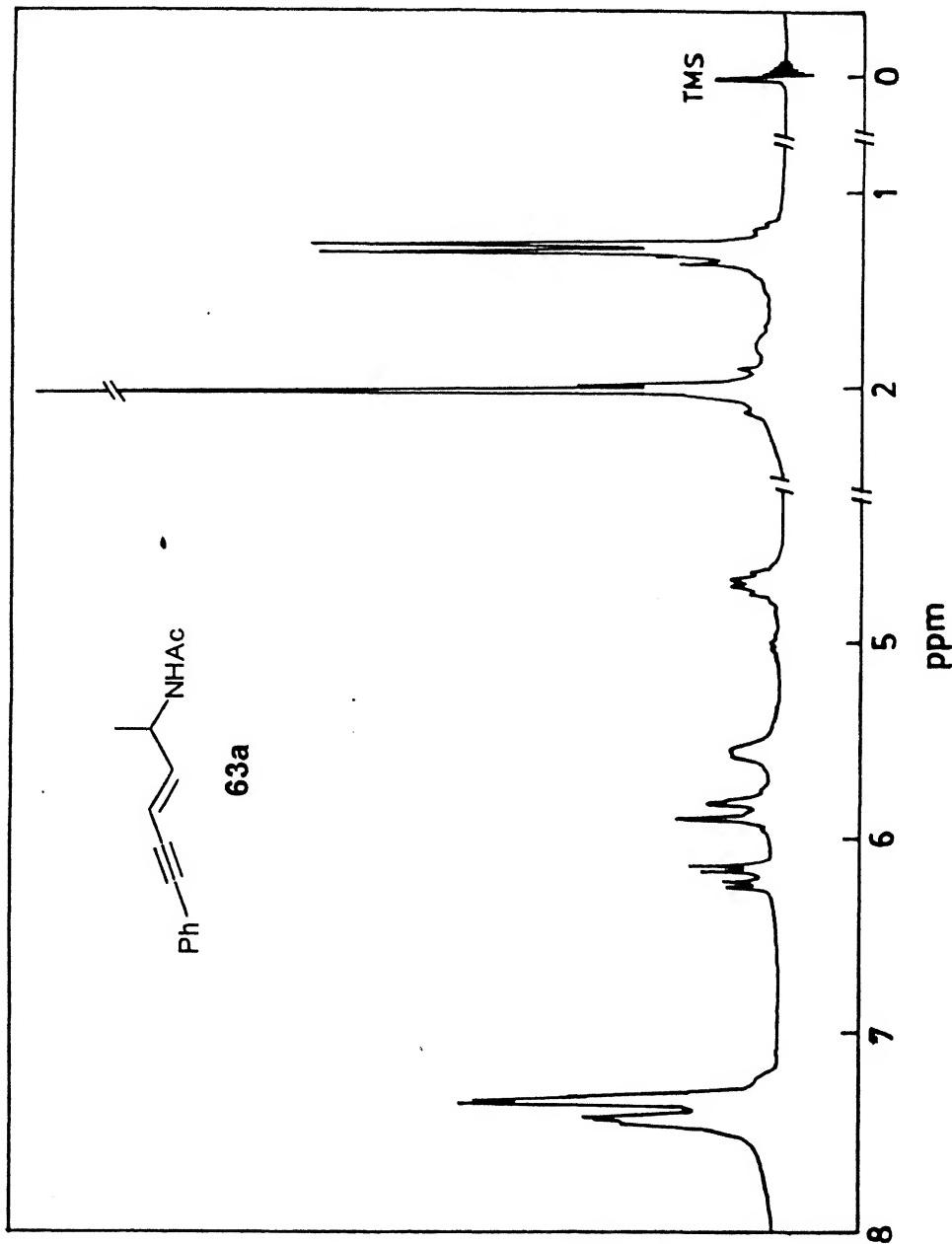
<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 0.9 (m, 3H), 1.0-1.4 (m, 11H), 1.8 (s, 3H), 1.85-2.1 (m, 2H), 4.2 (m, 1H), 5.4 (m, 2H), 6.2 (br d, 1H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 3310, 3060, 1630 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>23</sub>NO : C, 73.11; H, 11.67.

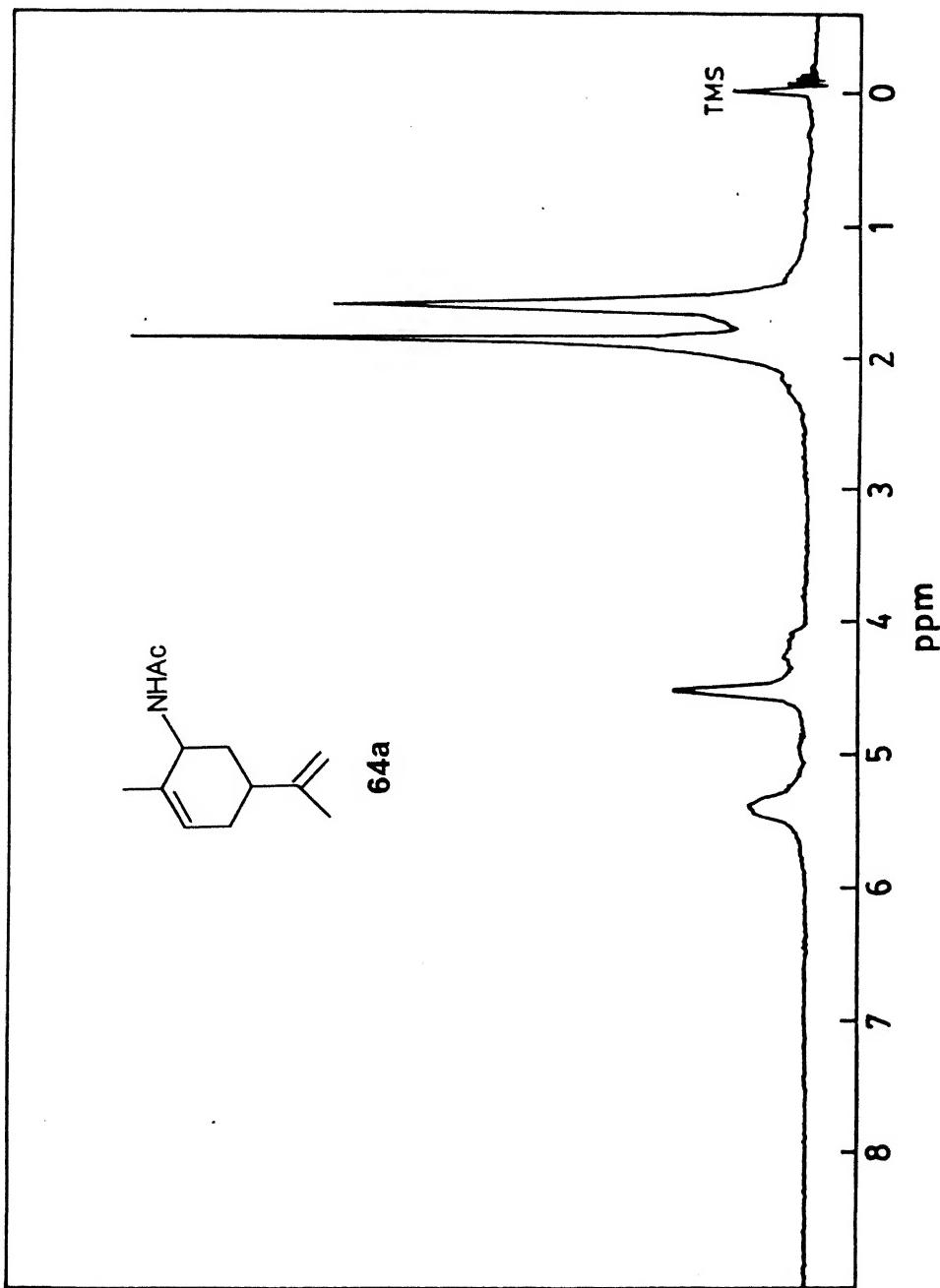
Found: C, 73.29; H, 11.75.

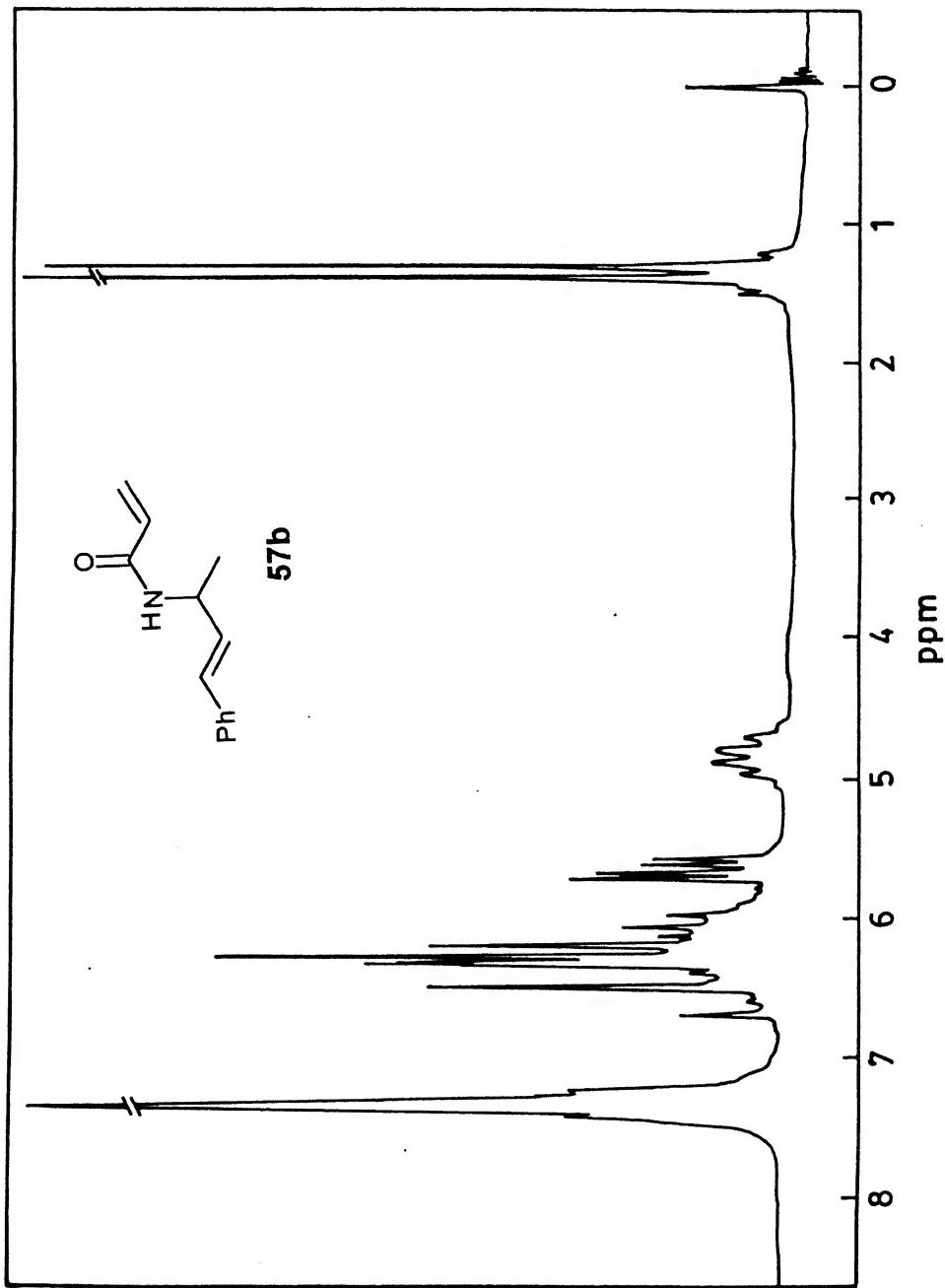


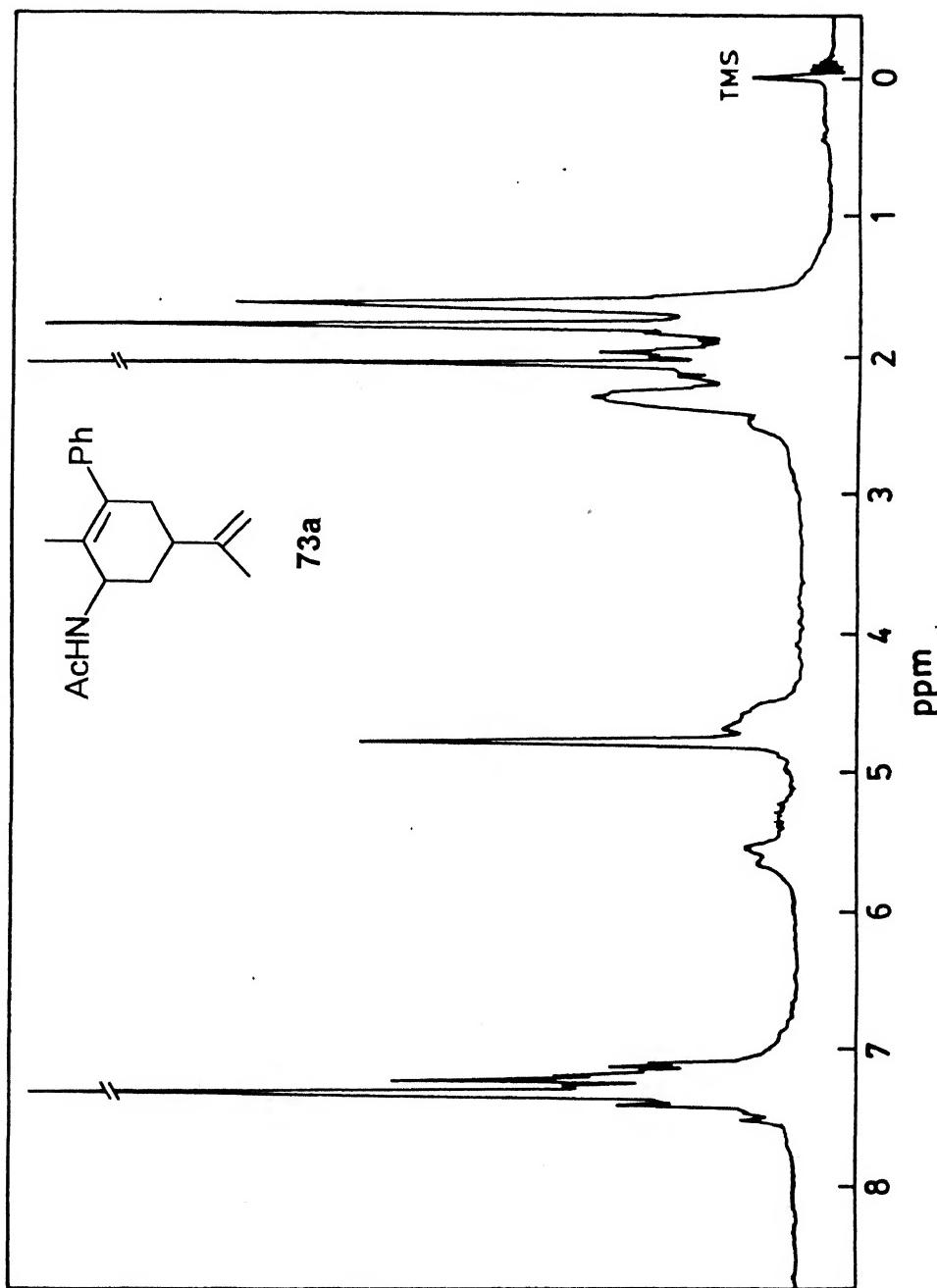


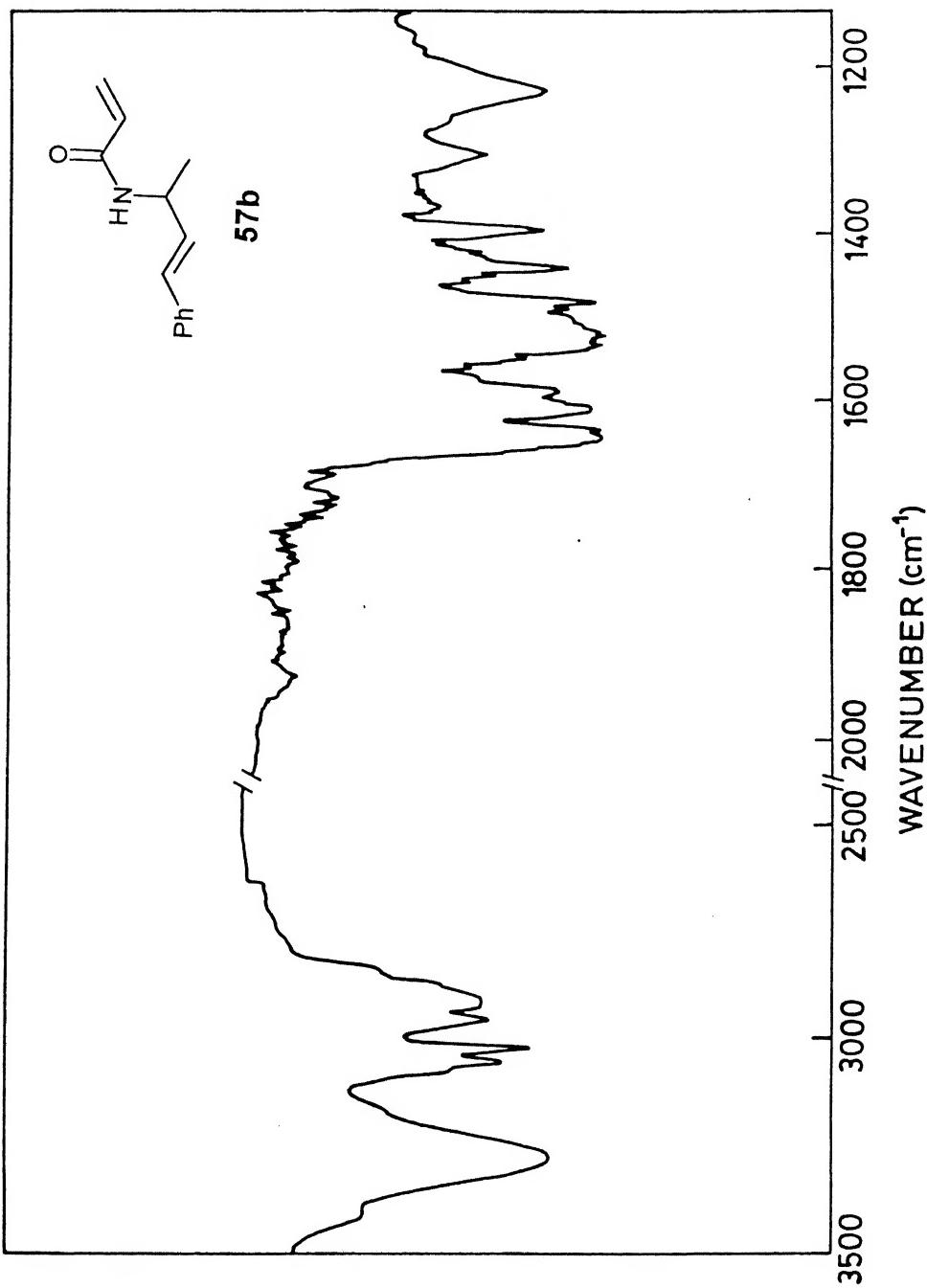
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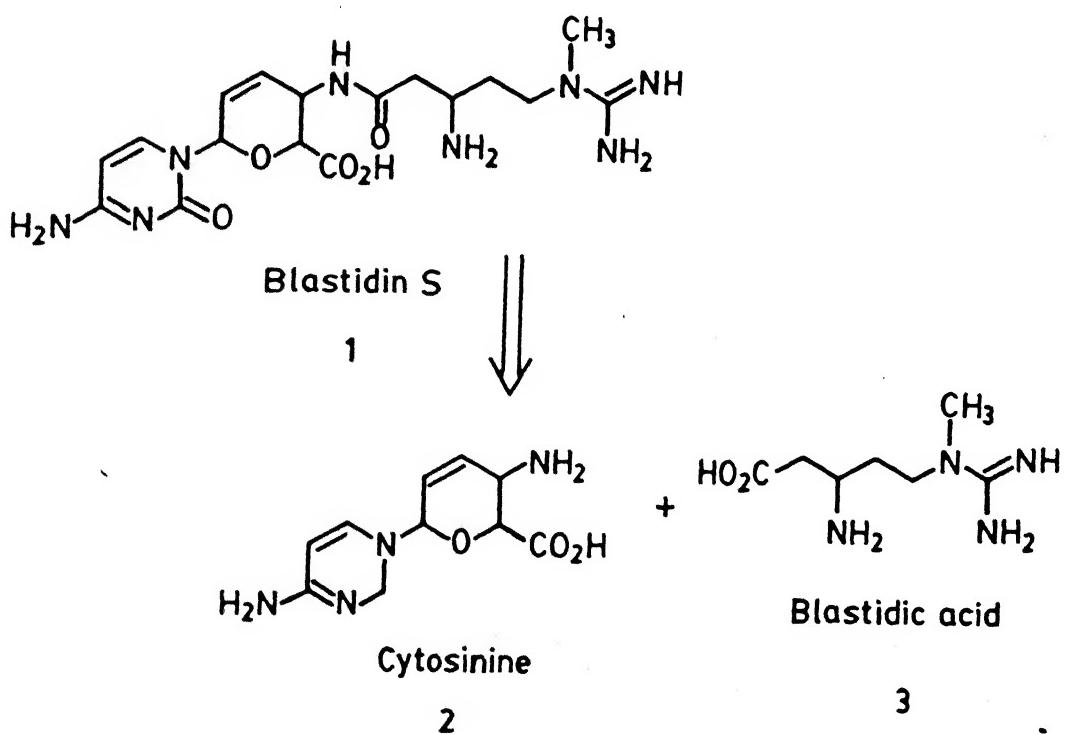
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## 2.1 INTRODUCTION

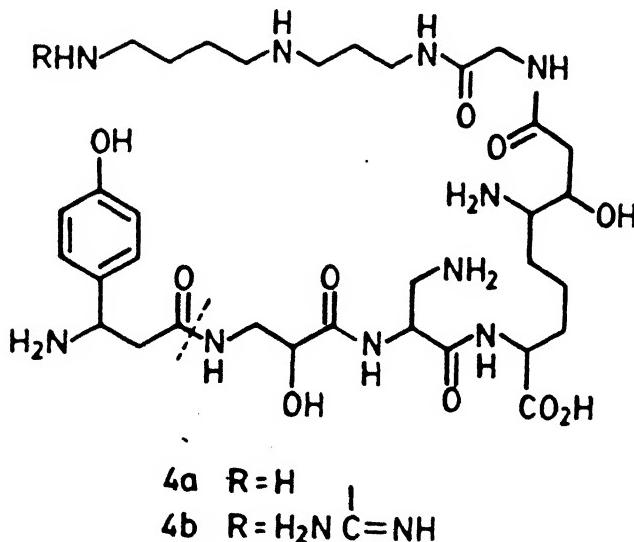
$\beta$ -Amino acids are potentially valuable for preparation of peptido mimetics<sup>1</sup>, functionalized  $\beta$ -lactams<sup>2</sup> and some naturally occurring compounds<sup>3</sup>. Although  $\beta$ -amino acids are much less abundant than their  $\alpha$ -analogues, few methods for the synthesis of racemic<sup>4</sup> and enantiomerically pure<sup>5</sup>  $\beta$ -amino acids have been developed.

$\beta$ -Aminoacids are important components of many naturally occurring compounds. For example, Blastidin S **1**, an antibiotic effective against rice blast disease was isolated from the culture broth of *Streptomyces griseochromogenes* by Yonehara and coworkers<sup>6,7</sup>. It consists of a pyrimidine nucleoside and  $\beta$ -amino acid named cytosinine **2** and blastidic acid **3** respectively<sup>8</sup> (Scheme 2.1).

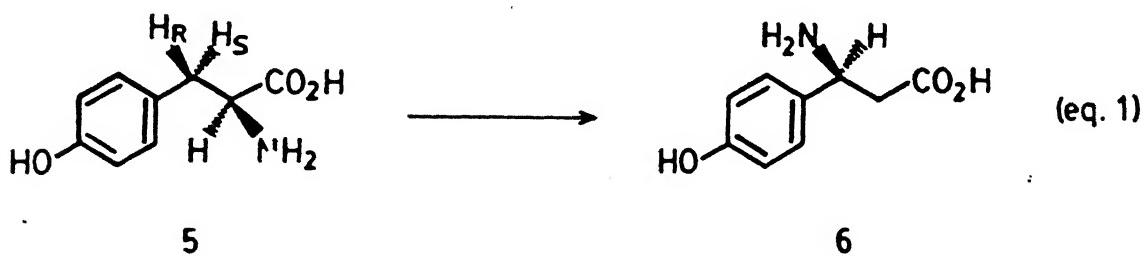


**Scheme 2.1**

Cultures of *Bacillus brevis* *V<sub>m4</sub>* produces two peptide antibiotics, edeine A and edeine B **4a-b**, that contain a group of novel amino acids<sup>3d,9</sup>

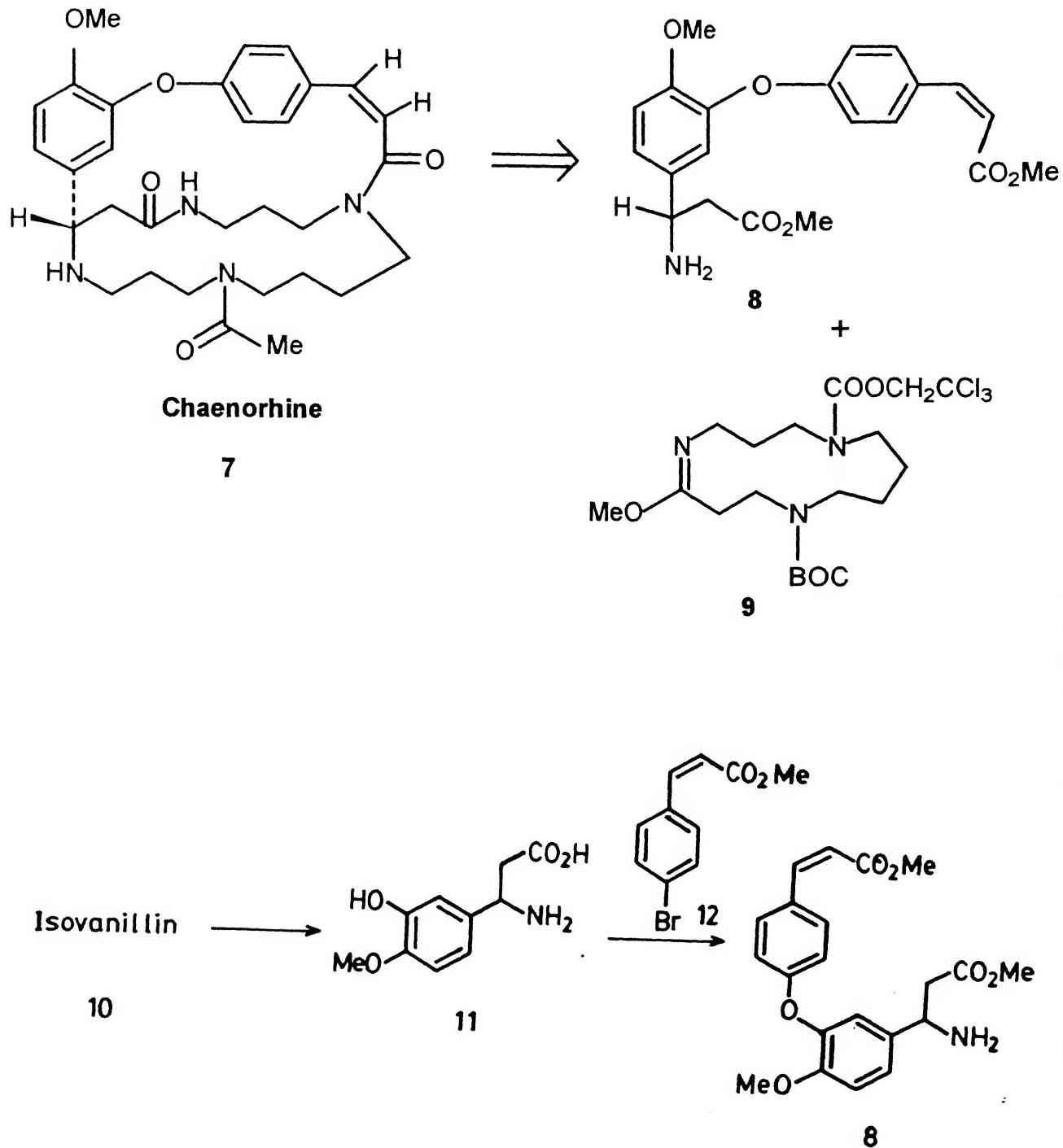


One of these amino acids is  $\beta$ -tyrosine **6** which is formed by the isomerization of  $\alpha$ -tyrosine **5** catalyzed by the enzyme tyrosine  $\alpha,\beta$ -mutase<sup>10</sup> (eq. 1).



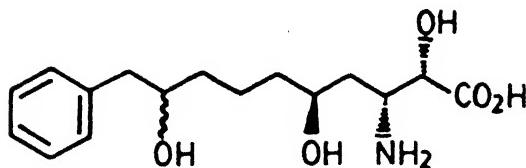
$\beta$ -Amino esters **8** are important components of Chaenorhine<sup>10</sup> **7**, a member of the polyamine family of alkaloids which was isolated from *Chaenorhinum origanifolium*. This  $\beta$ -amino ester was prepared by the sequence outlined in Scheme 2.2. The reaction of isovanillin **10** with ammonium acetate and malonic acid furnished the  $\beta$ -amino acid **11** which was then esterified and protected with BOC to yield the phenolic intermediate **12**. The copper phenoxide derived from this intermediate was coupled with methyl cis-p-bromocinnamate and removal of BOC yielded the  $\beta$ -amino ester<sup>11</sup> **8a**.

The  $\beta$ -amino acid, 3-amino-2,5,9-trihydroxy-10-phenyl decanoic acid (Ahda) **13** is an important component of cyclic peptide, Scytonemin A<sup>3c</sup>, which posses potent calcium antag-

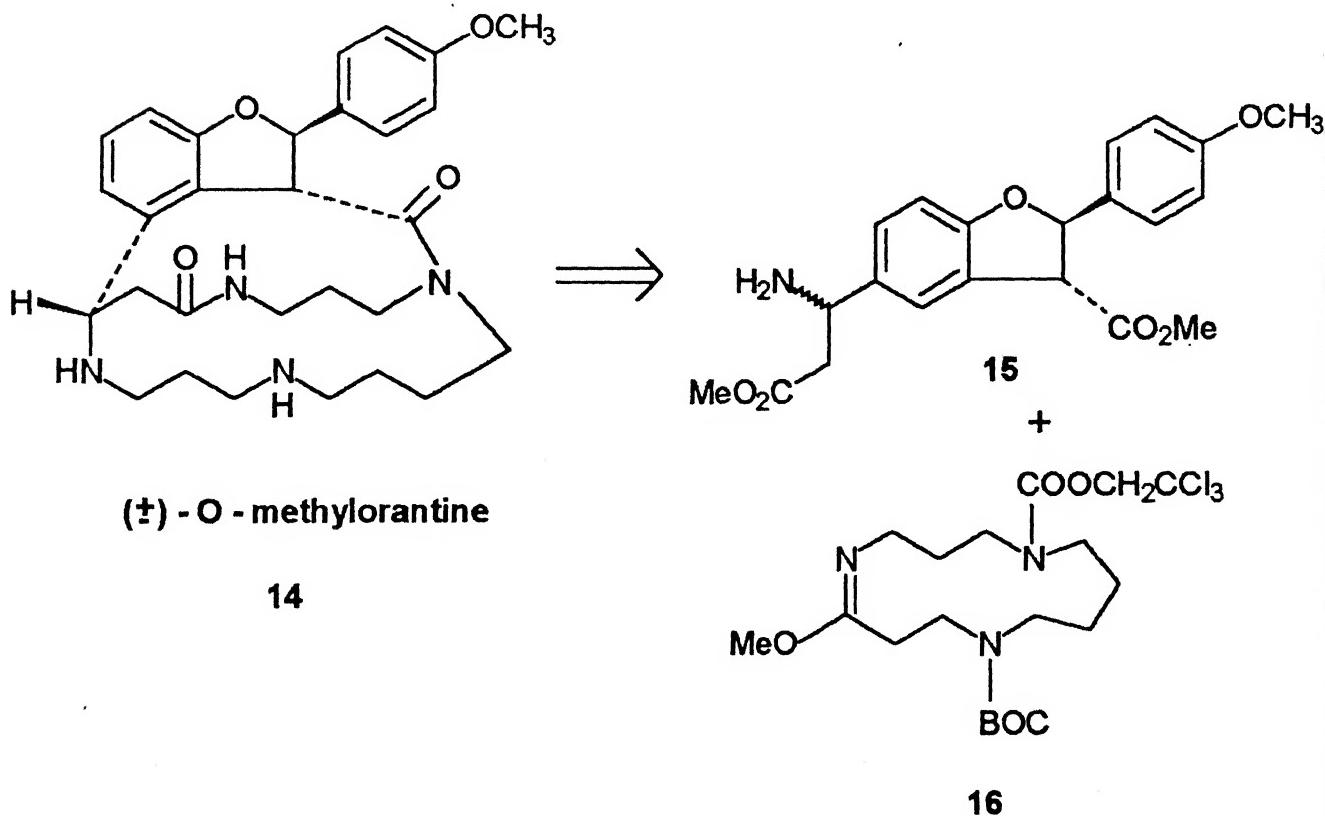


**Scheme 2.2**

onistic properties is a major metabolite of the cultured cyanophyte *scytonema* SP (Strain U-3-3). This amino acid **13** appears to be biologically related to 3-amino 9-methoxy 2,5,8-trimethyl 10-phenyl deca 4,6-dienoic acid, a novel amino acid component of cyanogenosin-LA, a potent hepatotoxin isolated from South African *Microcystic aeruginosa*.

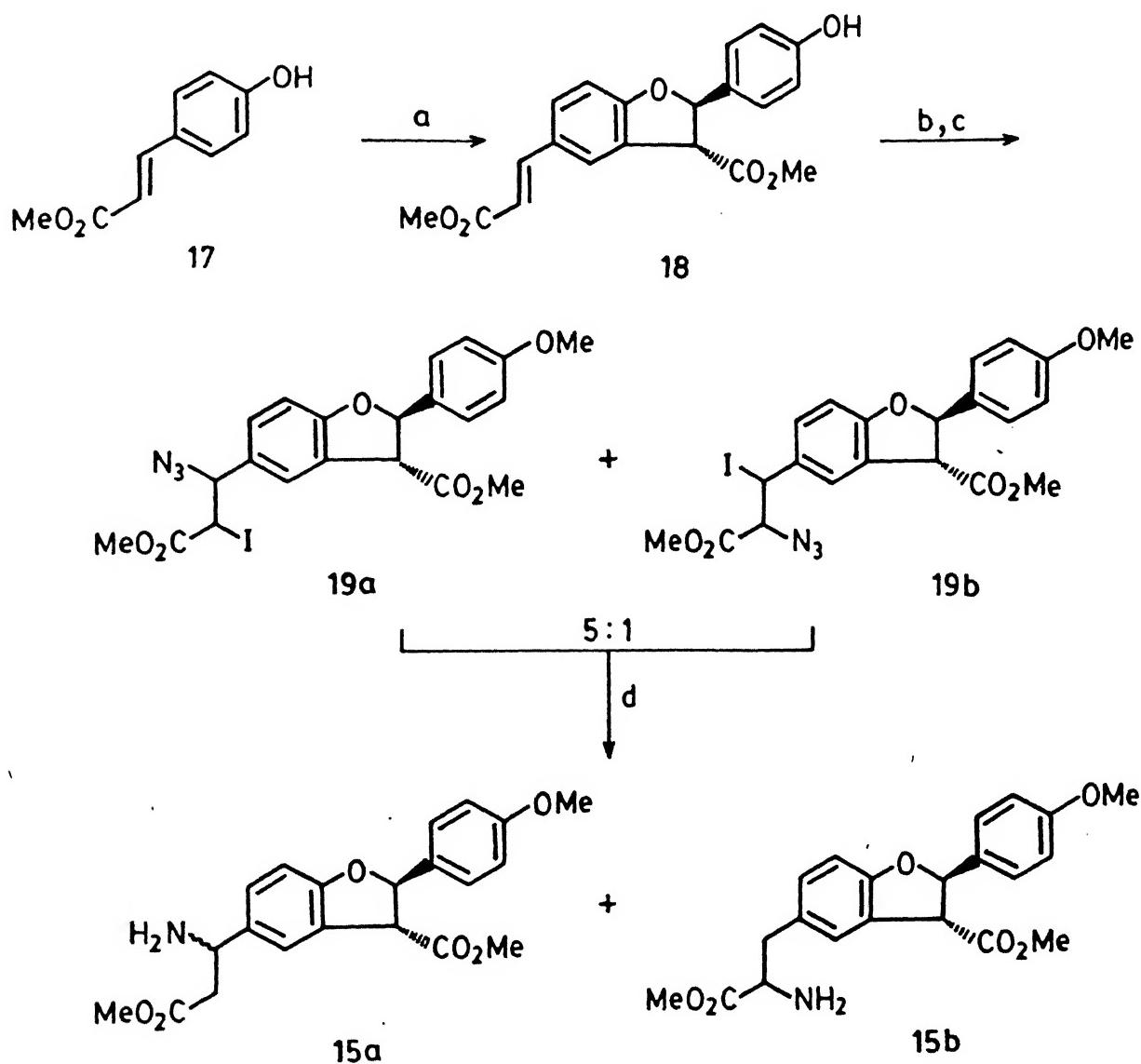


Another macrocyclic polyamine alkaloid ( $\pm$ )-O-methylorantine<sup>12</sup> **14** also contains the  $\beta$ -amino ester as an important component.



This  $\beta$ -amino ester **15** has been synthesized from methyl p-hydroxy cinnamate as shown in the Scheme 2.3.

$\beta$ -Amino acid, (2S, 3S, 8S, 9S) -3-amino 9-methoxy 2,6,8-trimethyl 10-phenyl 4,6-deca dienoic acid (Adda)<sup>13,14</sup> **20** is important for the hepatotoxicity of Nodularin<sup>15</sup> **20a** and microcystin-LR **20b** which are cyclic penta- and hepta peptides produced by cyanobacteria

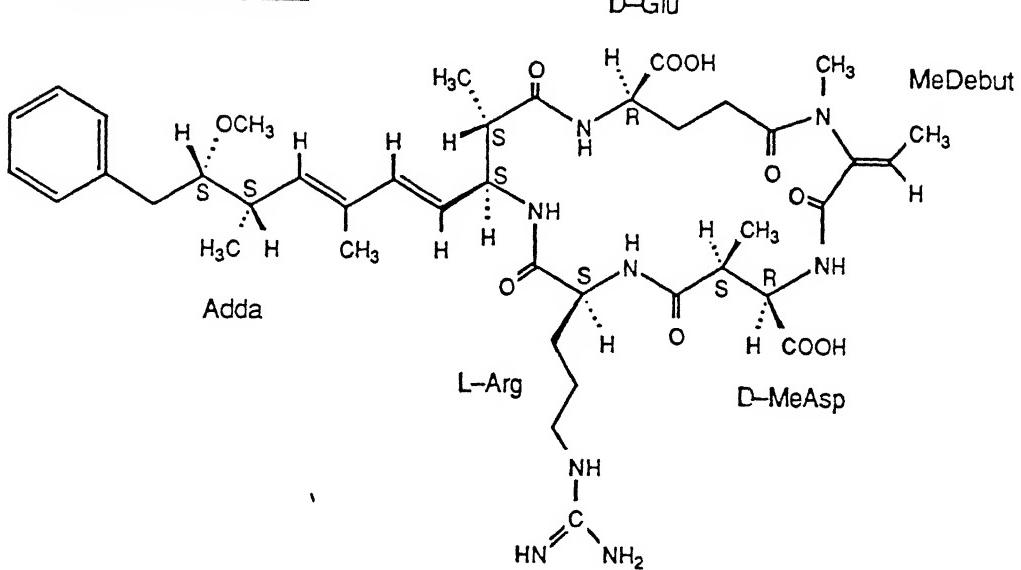


- a) Potassium ferricyanide,  $\text{Na}_2\text{CO}_3$ ,  $\text{CHCl}_3$ .
- b)  $\text{MeI} / \text{CH}_3\text{COCH}_3 / 25^\circ\text{C}$ .    c)  $\text{NaN}_3, \text{ICl} / \text{CH}_3\text{CN} / 0^\circ\text{C}$ .
- d)  $\text{Bu}_3\text{SnH}$ , (benzene /  $25^\circ\text{C}$  / 20h, benzene /  $80^\circ\text{C}$  / 1h).

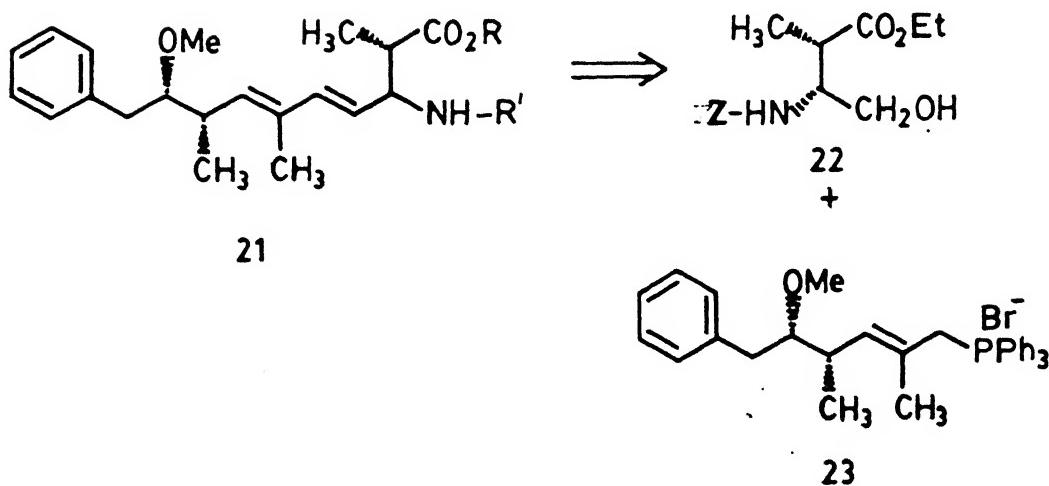
### Scheme 2.3

*Nodularia spumigena* and *Microcystis aeruginosa*, respectively. Retro-synthetically Adda can be divided into three parts (Scheme 2.4). First an amino acid part **22** (C-1 to C-4) which is derived from  $\gamma$ -butyrolactone, second **23** (C-5, C-6) and third is an aromatic part (C-7 to C-10).

### Nodularia spumigena

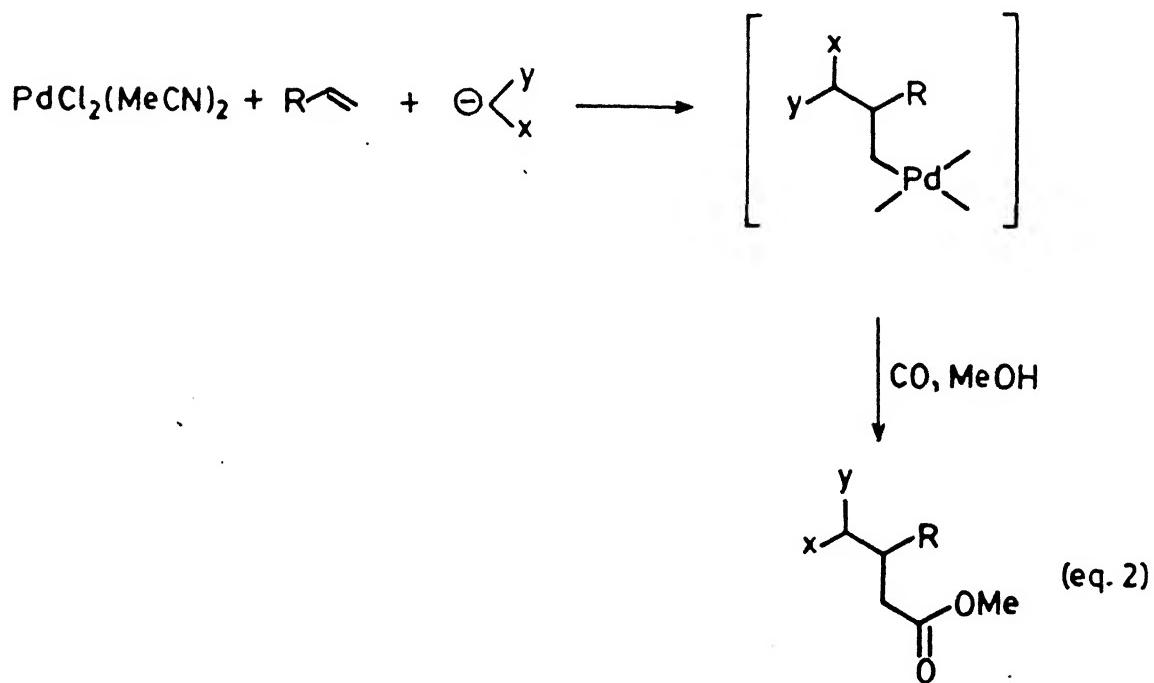


#### Nodularin (hepatotoxin)



### Scheme 2.4

Olefins coordinated to Palladium(II) salts are generally reactive towards nucleophiles<sup>16</sup> and undergo facile alkylation by stabilized carbanions<sup>17</sup> to produce unstable ( $\sigma$ -alkyl)- palladium(II) complexes. These readily undergo carbonmonoxide insertion<sup>18</sup>, to result in overall *carboacylation* of the alkene (eq. 2). With enamides<sup>19</sup> as the olefin ( $R = NHCOR$ ) attack occurs exclusively  $\alpha$  to the nitrogen, and carbonylation produces highly functionalized

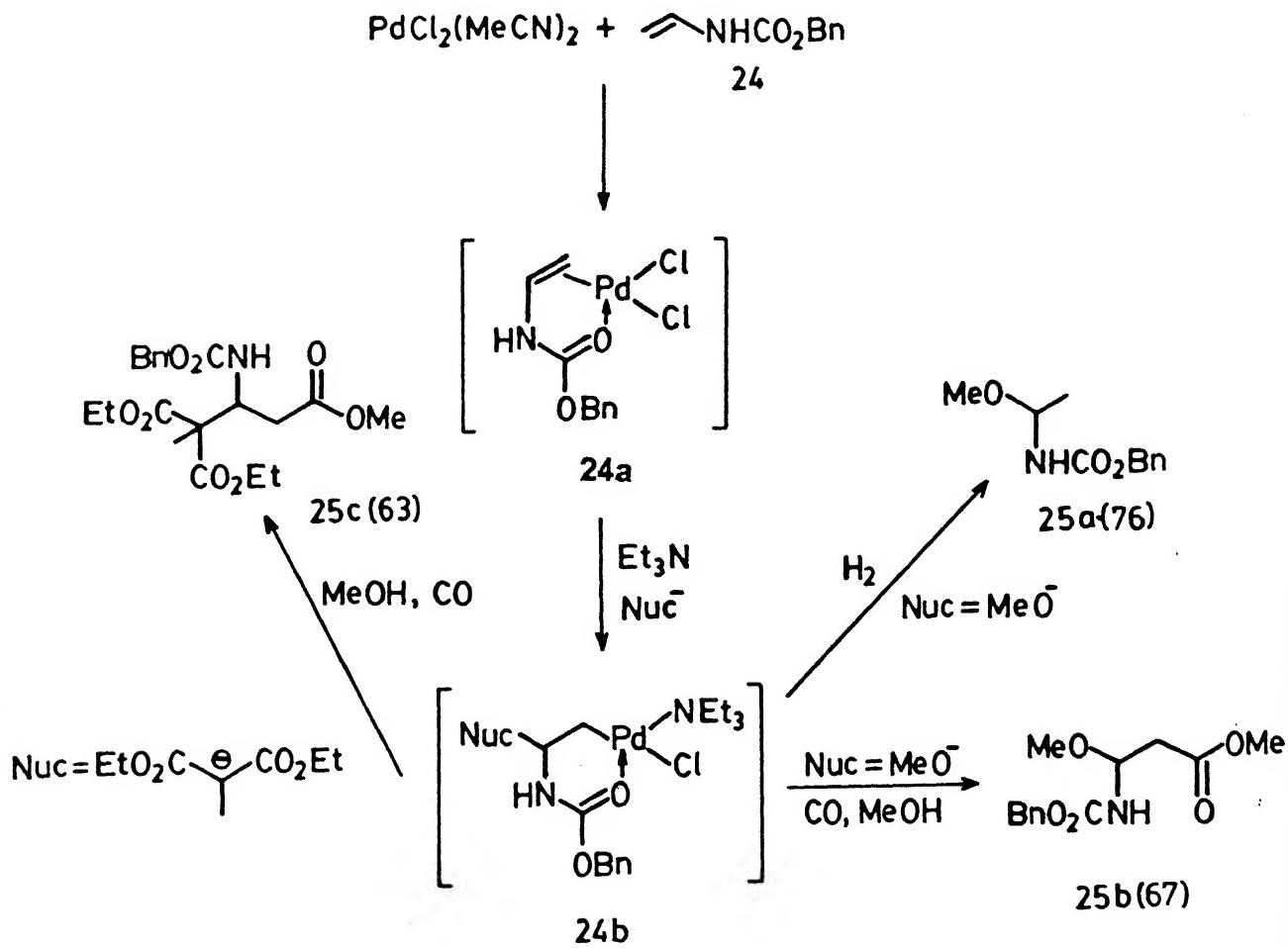


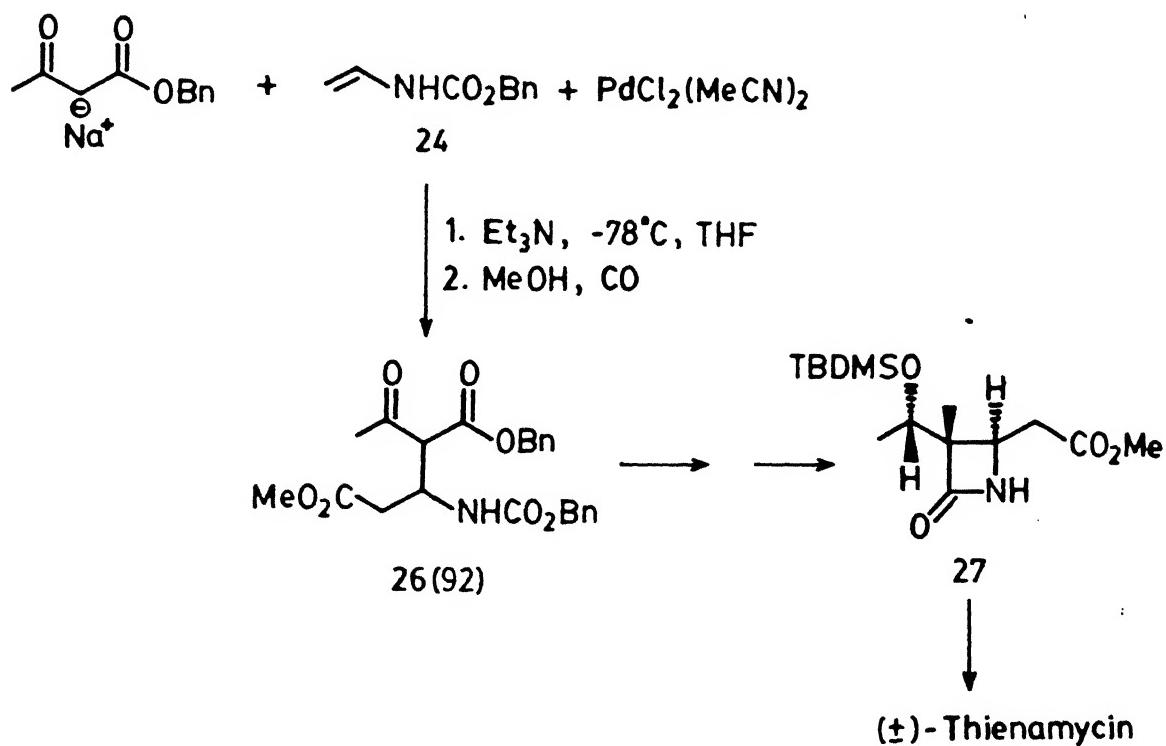
$\beta$ -amino acid derivatives. These  $\beta$ -amino acids can easily be converted to the  $\beta$ -lactams which are potentially biologically active compounds.

The enamide substrate i.e., benzyl vinylcarbamate<sup>20</sup> **24** smoothly underwent alkoxylation and alkylation in the presence of palladium(II) to produce unstable ( $\sigma$ -alkyl) palladium(II) complexes **24a-b**. These underwent cleavage with hydrogen without debenzylation or underwent carbonylation under mild conditions (Scheme 2.5), to produce the functionalized carbamates **25a-c** in overall good yield.

Palladium assisted carboacylation of benzyl vinylcarbamate with benzyl acetoacetate was very efficient producing the highly functionalized keto diester carbamate **26**, in excellent yield, as a  $\sim 1:1$  mixture of diastereoisomers, in one step. This keto ester was converted to  $\beta$ -lactam **27**, which is having the relative stereochemistry of ( $\pm$ )-epithienamycin<sup>21</sup> (Scheme 2.6).

The  $\beta$ -amino acids are valuable intermediates in the field of  $\beta$ -lactam synthesis and effective tools for peptide modifications. However, the preparation of chiral  $\beta$ -amino acids is known to be tricky and derivatives, being not homologous to the natural  $\alpha$ -amino acids are scarcely assessable enantiomerically pure.

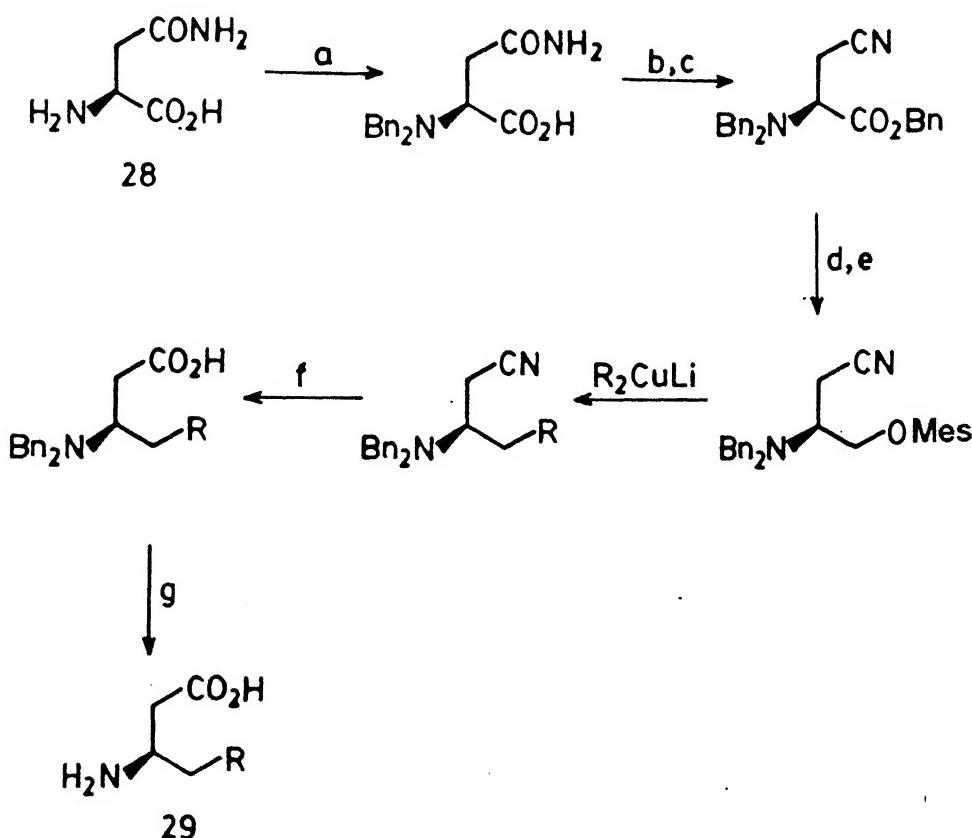
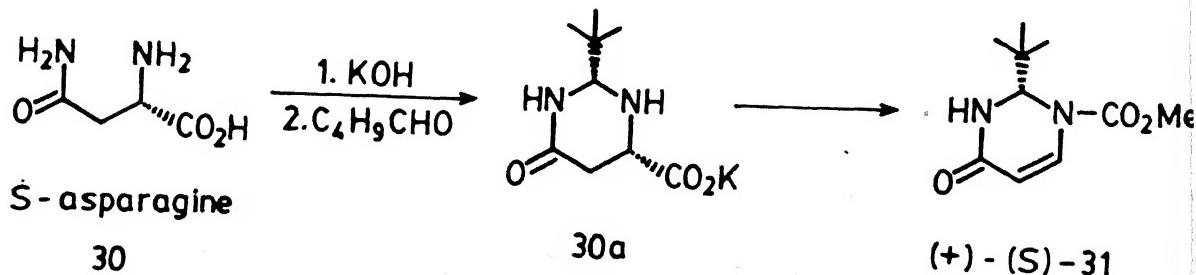
Scheme 2.5

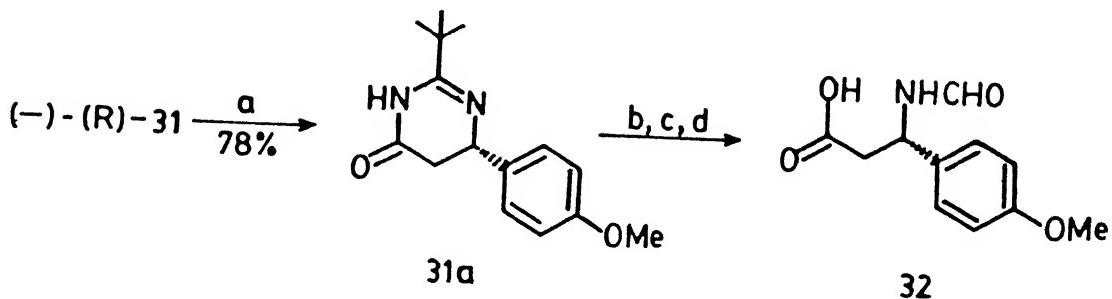
**Scheme 2.6**

Enantiomerically pure  $\beta$ -amino acids **29** can be prepared from L-asparagine<sup>22</sup> **28** via the activated  $\beta$ -homoserine equivalent (Scheme 2.7).

Enantiomerically pure aromatic  $\beta$ -amino acids<sup>23</sup> have been synthesized by using a heterocycle **31** as a reagent. This reagent was prepared from S-asparagine **30** as shown in the Scheme 2.8. Treatment of (-)-(R)- **31** with 4-iodoanisole and triethylamine in DMF in the presence of palladium acetate and tri- O- tolylphosphine gave the product **31a** which was on reduction followed by hydrolysis affords (S)- $\beta$ -tyrosine- O- methyl ether hydrochloride in 85% yield. This on formylation affords the N-formyl derivative **32** (Scheme 2.9).

Seebach and coworkers<sup>24</sup> have synthesized the  $\alpha$ - substituted  $\beta$ -amino acids by the hydrolysis of 2- tert- butylperhydropyrimidin -4-one derivative **34**. An inexpensive and achiral amino acid  $\beta$ -alanine was converted efficiently into the recemic tetrahydropyrimidinone **34**.

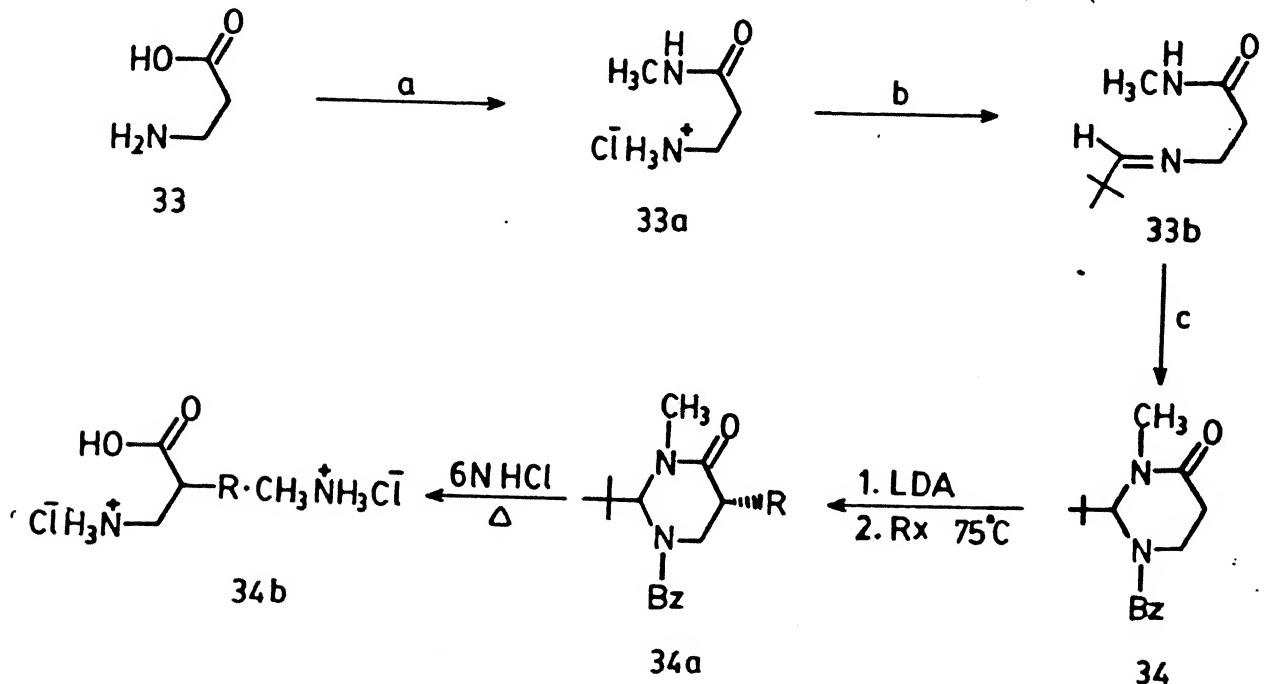
**Scheme 2.7****Scheme 2.8**



- a)  $\text{Pd}(\text{OAc})_2$  (1%) /  $\text{PAr}_3$  (2%) /  $\text{MeOC}_6\text{H}_4\text{I}$  /  $\text{NEt}_3$  / DMF,  
 b)  $\text{NaBH}_4$  /  $\text{H}_3\text{O}^+$ , c) 3N HCl, d)  $(\text{Ac})_2\text{O}$  /  $\text{HCO}_2\text{H}$ .

**Scheme 2.9**

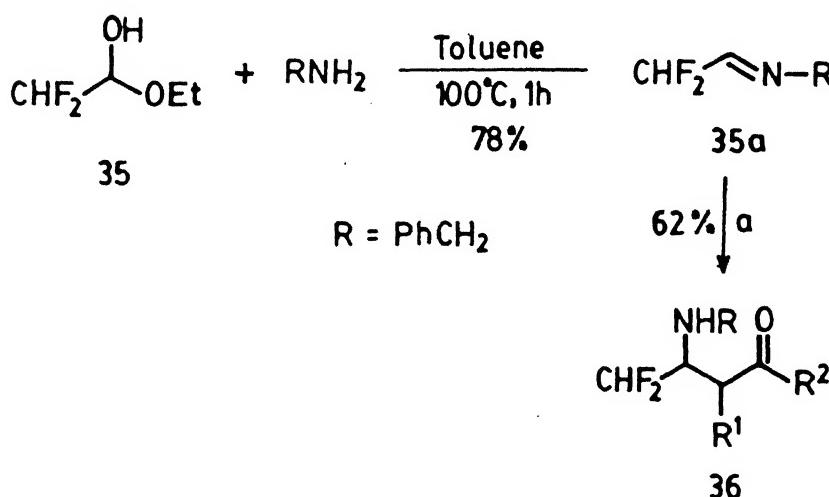
Highly diastereoselective alkylation products were formed by treatment of enolate 34a -Li generated with LDA in THF with halides RX at  $-75^\circ \text{C}$ . These pyrimidinone adducts 34a were converted to the  $\alpha$ - substituted  $\beta$ -amino acids 34b by acid hydrolysis (Scheme 2.10).



- a) i)  $\text{Me}_3\text{SiCl}$  /  $\text{CH}_3\text{OH}$ ; ii)  $\text{MeNH}_2$  /  $\text{CH}_3\text{OH}$   
 b) t-BuCHO /  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $(\text{PhCO})_2\text{O}$ ,  $180^\circ \text{C}$ , 8h.

**Scheme 2.10**

$\beta$ -(difluoromethyl)- $\beta$ -amino acids are biologically important compounds because of their property as suicide inhibitors. Particularly  $\beta$ -(difluoromethyl)- $\beta$ -alanine (3-amino-4,4-difluorobutanoic acid) is a potent in vitro and in vivo inhibitor of GABA-T<sup>25</sup>, however, its synthesis usually requires toxic reagents or multiple synthetic steps. Kitazume et al<sup>26</sup>. have developed a versatile method by which this compound can be prepared very easily. Hemiacetal **35** was smoothly transformed into difluoromethylated imines **35a** via the reaction of primary amines<sup>27</sup>. The reaction of **35a** with a silyl ketene acetal in the presence of TBAF gave a precursor of  $\beta$ -(difluoromethyl- $\beta$ -alanine) in one step (Scheme 2.11).

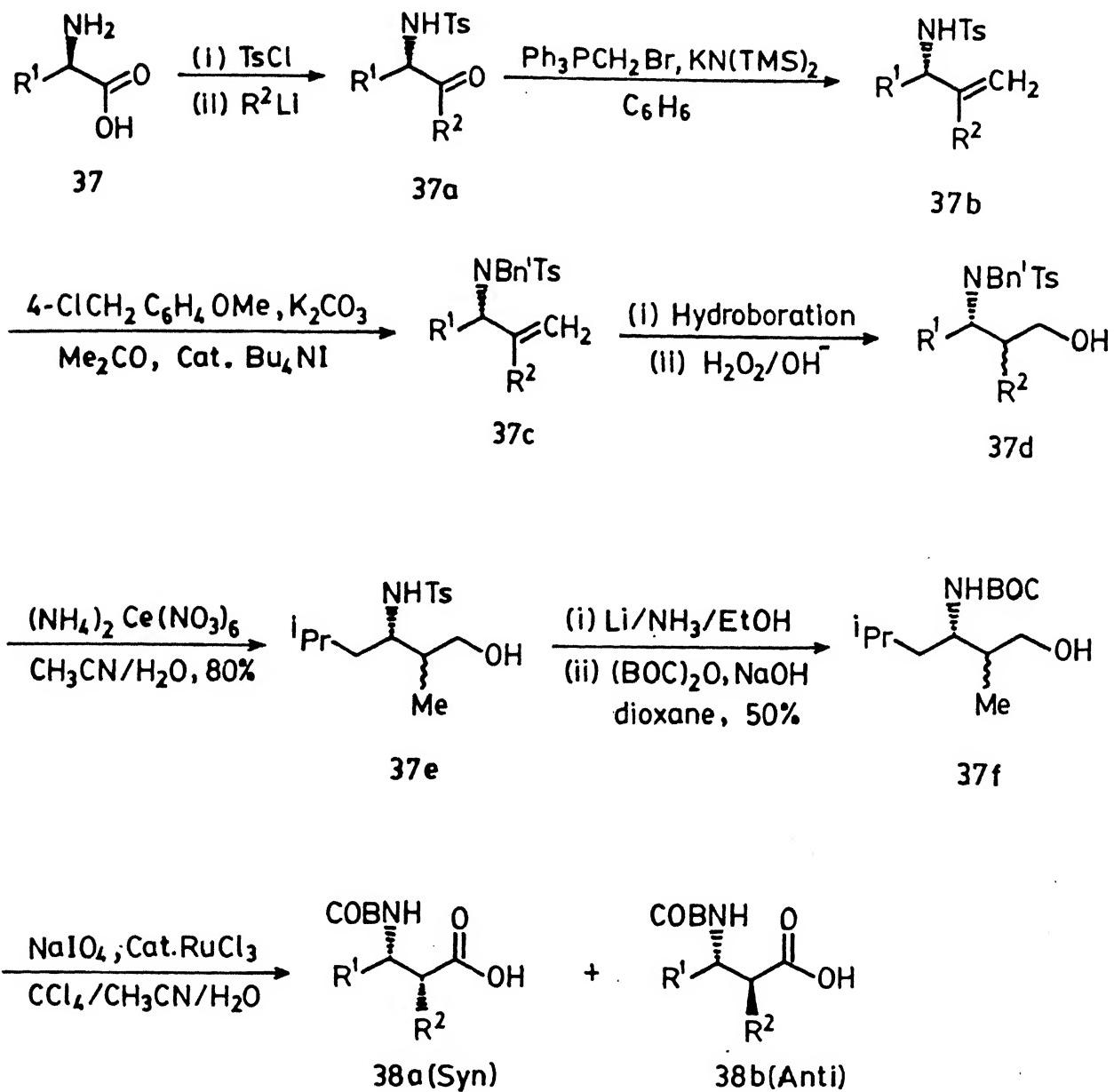


**Scheme 2.11**

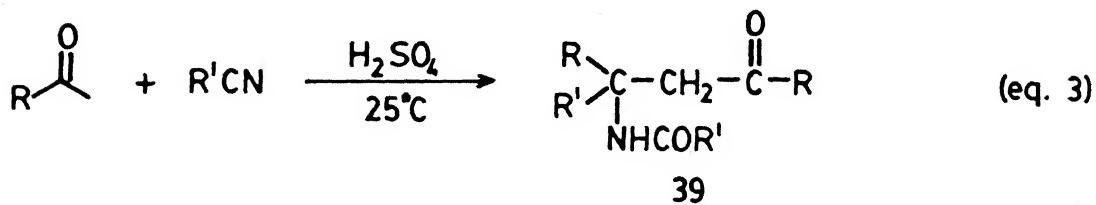
Disubstituted  $\beta$ -amino acids<sup>28</sup> **38** can be synthesized with high absolute and relative stereochemical purity from naturally occurring  $\alpha$ -amino acids, as shown in Scheme 2.12. Hydroboration/oxidation of allylic amines **37c** is the key step in this reaction. Different selectivity was observed with  $\text{BH}_3$  and 9-BBN. Hydroboration with  $\text{BH}_3$  gave anti product, whereas 9-BBN gave the syn product<sup>29</sup>. High diastereoselectivity was also observed for the anti-selective hydroboration of the dibutyl substituted system **37c**.

In 1959, Khorlin and coworkers<sup>30</sup> have synthesized the  $\beta$ -acylamino ketones by the condensation of ketones with nitriles in the presence of concentrated sulfuric acid (eq. 3).

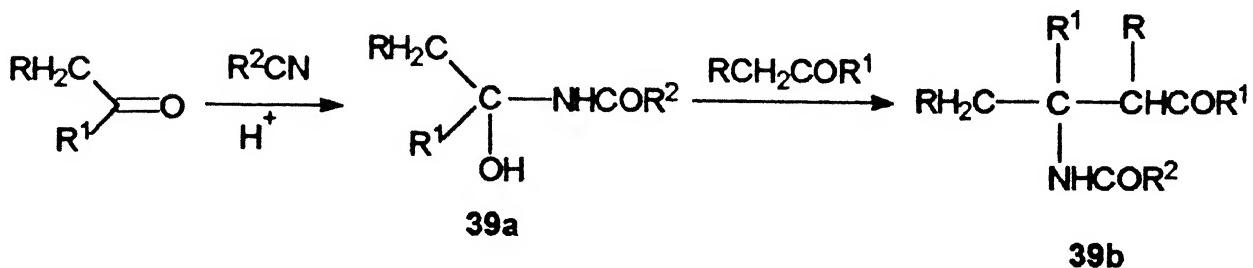
The condensation of ketones with nitriles, leading to the formation of  $\beta$ -acylamino ketones, proceeds via initial formation of the hydroxymethylamide **39a** which reacts with a second



Scheme 2.12

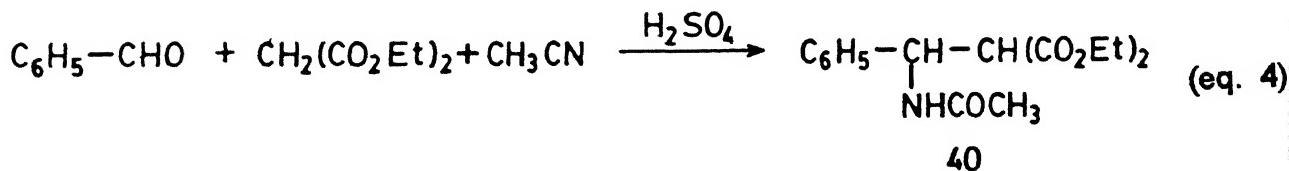


molecule of ketone by acylaminomethylation type of reaction, giving the acylamino ketone **39b** (Scheme 2.13).

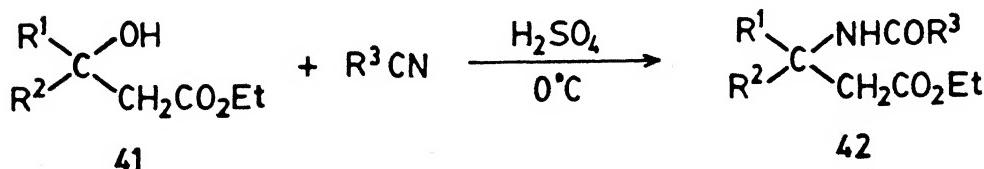
**Scheme 2.13**

It is interesting to note that acetophenone and its substituted analogues (p-methyl and p-methoxy acetophenone) gave high yields of condensation products with acetonitrile, benzyl cyanide and even with acrylonitrile, whereas propiophenone does not react with nitriles under these conditions.

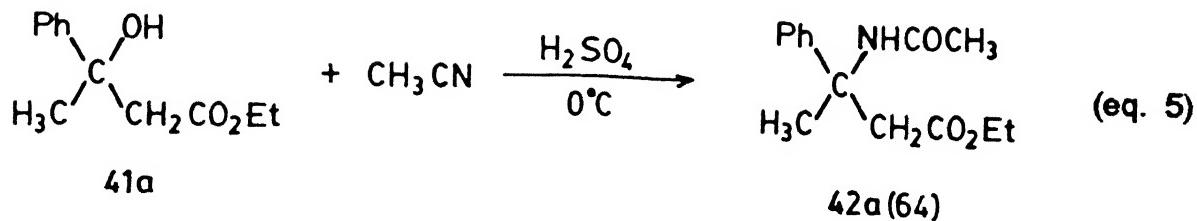
Benzaldehyde and malonic ester condensed with acetonitrile in the presence of conc.  $\text{H}_2\text{SO}_4$  to give the ethyl ester of 1-carbethoxy-2-phenyl-2-acetamido propionic acid in good yield (eq. 4).



Jansen and Taub<sup>31</sup> synthesized the  $\beta$ -acylamino esters by Ritter reaction<sup>32</sup>. Hydroxy esters **41** react with nitrile in the presence of concentrated sulfuric acid to give the  $\beta$ -acylamino esters **42** in good yields (Scheme 2.14). For example, ethyl 3-acetamido 3-phenyl butyrate

**Scheme 2.14**

**42a** has been prepared from ethyl 3-hydroxy 3-phenyl butyrate **41a** and acetonitrile by using this methodology (eq. 5).

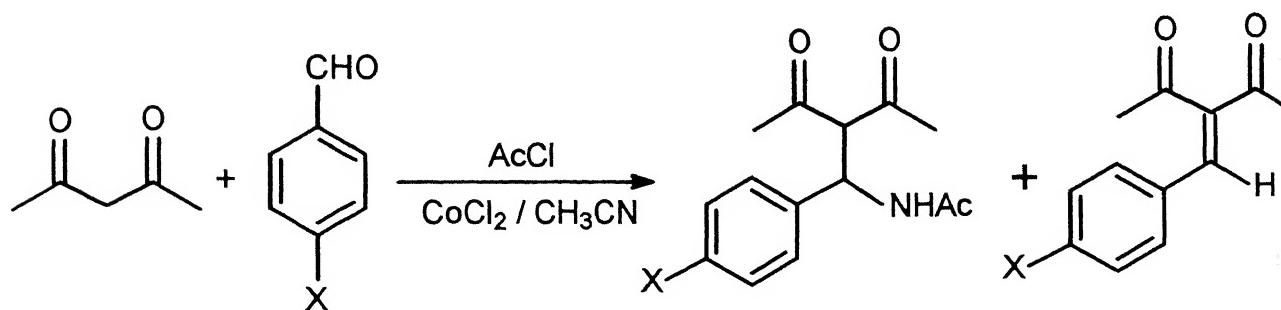


The foregoing section has clearly demonstrated the importance of the  $\beta$ -amino acids or ketones. In view of this, we have undertaken a project for developing a new route for the synthesis of this class of compounds. We now show that  $\beta$ -amino ketones or esters can be prepared in one pot by three component coupling involving ketones or ketoesters, aldehydes and acetonitrile.

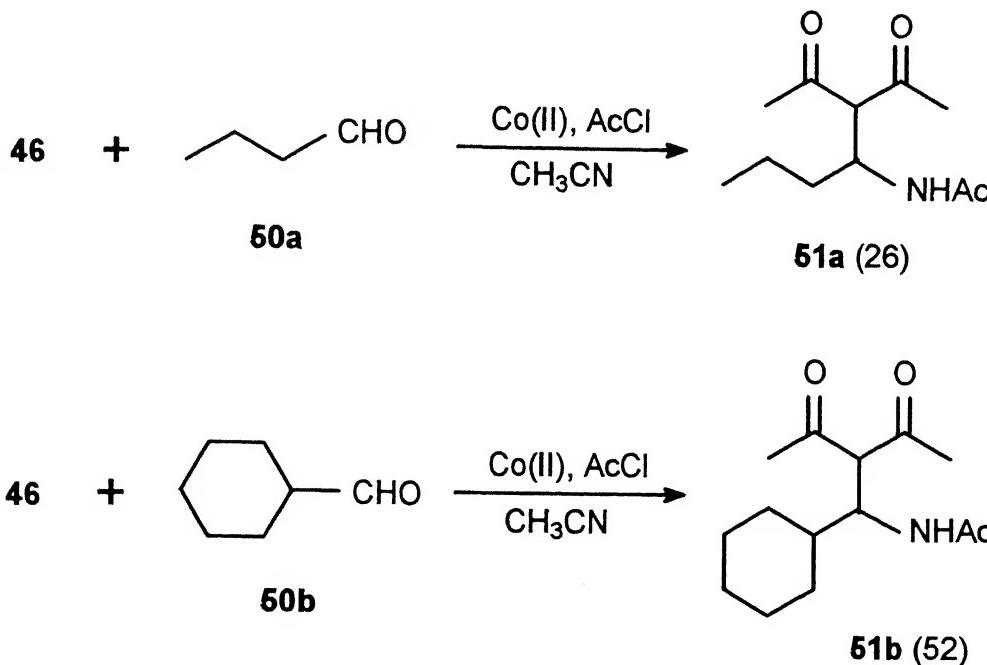
## 2.2 PRESENT STUDY

It has already been established in the previous section that  $\beta$ -keto amides or  $\beta$ -amino esters are versatile intermediates for the synthesis of a wide range of naturally occurring peptides and as mimics for various isosters. Therefore development of a general route to this class of compounds is a highly appropriate and challenging task. Although novel methodologies exist for the synthesis of  $\beta$ -keto amides and amino acids an efficient catalytic route to their access is still lacking. We now describe a novel route which follows the chemistry of an aldol type of condensation<sup>33</sup>. However, the coupling partners here are two different carbonyl compounds in the presence of acetonitrile. Metal catalyzed coupling between enolisable ketones and aldehydes has seldom been used to achieve the formation of aldol or related products. Although the reaction between silyl enolether and an aldehyde or the corresponding acetals is known to proceed readily under the influence of a metal catalyst<sup>34</sup>. We have recently observed that the aldehydes **43** react with acetyl chloride in acetonitrile under the influence of catalytic amount of cobalt(II) chloride to afford  $\alpha$ -acetoxy amides **45** in quantitative yields (Scheme

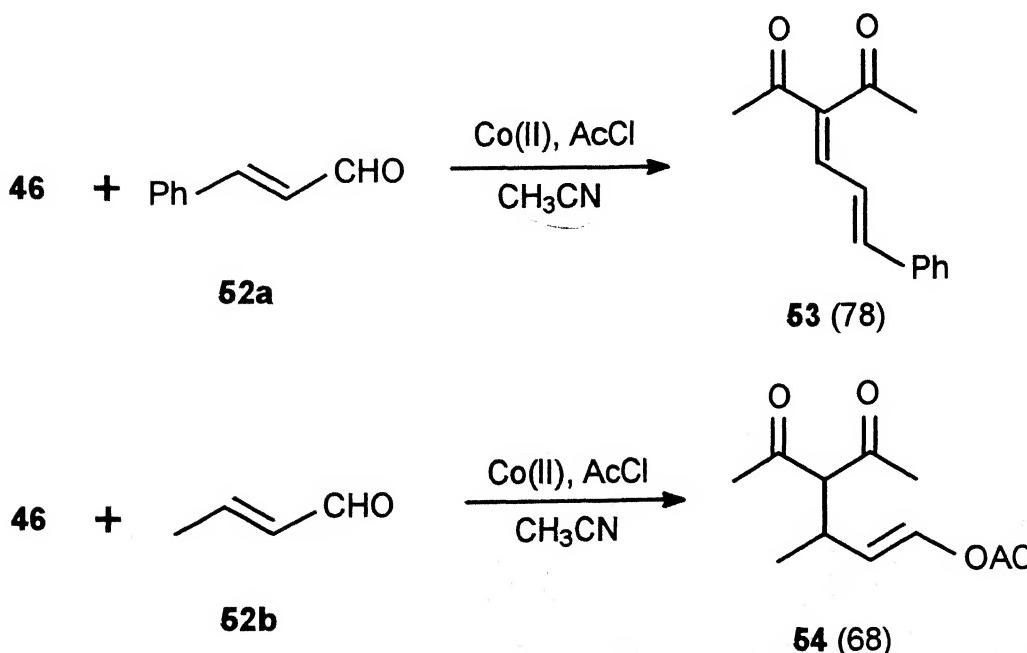
**Table 2.1 : Cobalt (II) Catalyzed Reaction of p- Substituted Benzaldehyde with Acetylacetone in Acetonitrile.**



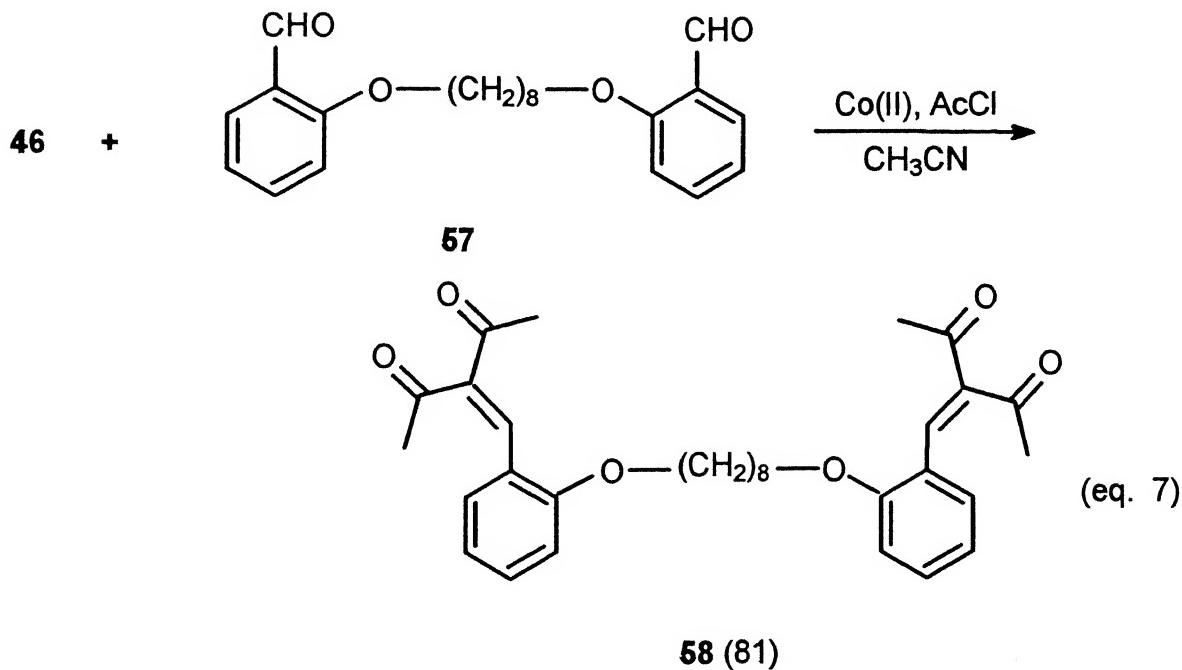
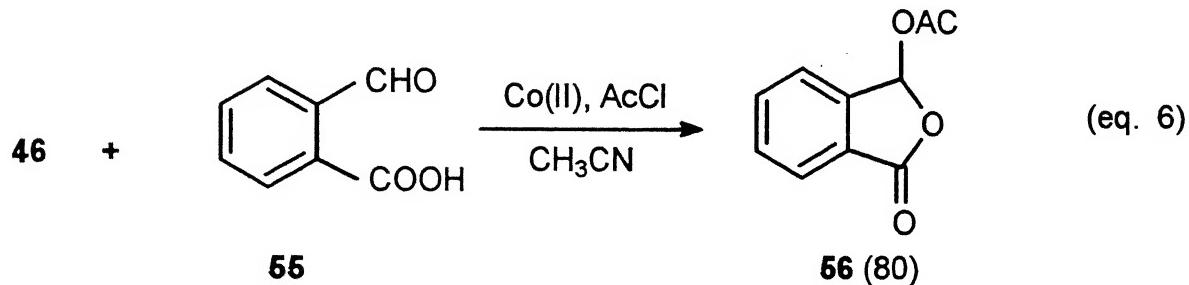
Entry	Aldehyde	X	48	Yield (%)	49
1	47a	H	48a (39)		49a(23)
2	47b	Cl	48b(53)		-
3	47c	$\text{NO}_2$	48c(48)		49b(26)
4	47d	$\text{CO}_2\text{Me}$	48d(62)		-
5	47e	Me	48e(29)		49c(23)
6	47f	$\text{OMe}$	48f(23)		49d(53)
7	47g	OH	48g(27)		49e(54)
8	47h	$\text{NMe}_2$	-		49f(69)

**Scheme 2.16**

The reaction with the  $\alpha$ ,  $\beta$ -unsaturated aldehyde and acetylacetone is highly substrate dependent. Thus the reaction with cinnamaldehyde **52a** provided the dienone **53** exclusively in high yield, whereas the reaction with crotonaldehyde **52b** gave an entirely different product, a vinyl acetate **54** (Scheme 2.17). This difference between two enals is presently unclear. It

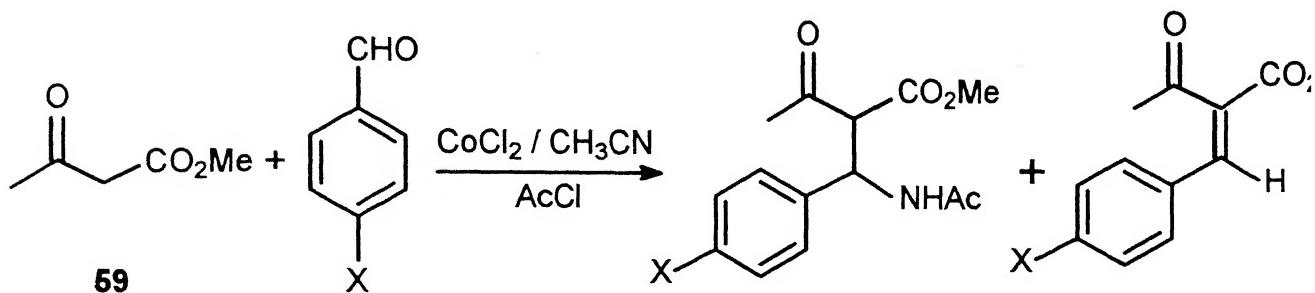
**Scheme 2.17**

is also worth noting that neither of these reactions provide the formation of any amides. There was no reaction between acetylacetone and phthalaldehydic acid **55**, however, the latter was converted to the corresponding benzofuranone derivative **56** (eq. 6). Once again this behaviour is quite surprising. On the other hand, dialdehyde **57** underwent very clean reaction to give **58** in very high yield (eq. 7). Once again the absence of any amide is rather surprising.



The reaction of different p-substituted benzaldehydes and methyl acetoacetate is presented in table 2.2. It is very clear from table 2.2 that the reaction with methyl acetoacetate **59** also provides a mixture of  $\beta$ -ketoamides **60a-d** and  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds **61a-d**. Once again the results presented in table 2.2 indicate that the substitution at p-position has very little influence on the formation of these two products. These amides were formed as a

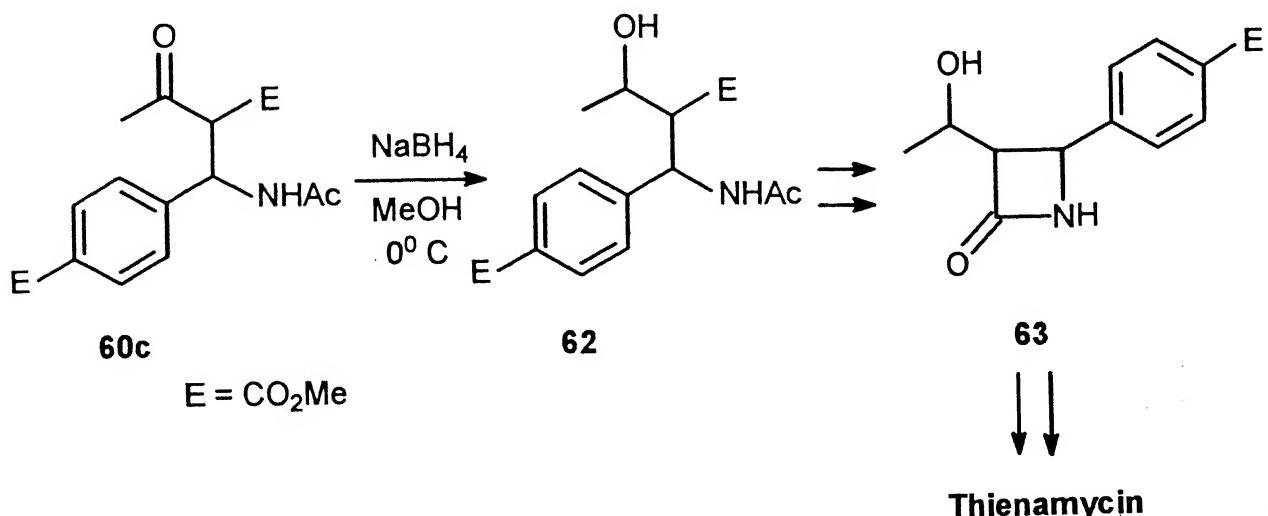
**Table 2.2 : Cobalt (II) Catalyzed Reaction of p- Substituted Benzaldehyde with Methyl Acetoacetate in Acetonitrile.**



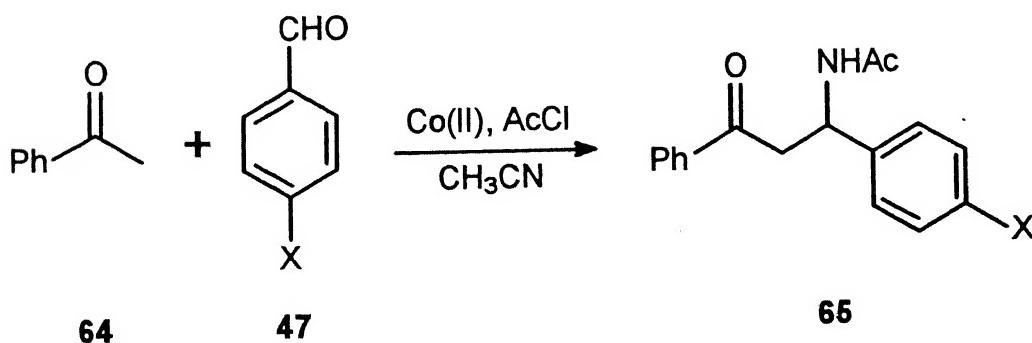
Entry	Aldehyde	X	60	Yield (%)	61
1	<b>47b</b>	Cl	<b>60a</b> (41)		<b>61a</b> (12)
2	<b>47c</b>	$\text{NO}_2$	<b>60b</b> (31)		<b>61b</b> (54)
3	<b>47d</b>	$\text{CO}_2\text{Me}$	<b>60c</b> (44)		<b>61c</b> (17)
4	<b>47e</b>	Me	<b>60d</b> (26)		<b>61d</b> (45)

mixture of two diastereomers and there was no selectivity observed in these reactions. No attempt was made to separate these diastereomers. The amides derived from aldehyde and methyl acetoacetate are good precursors for the synthesis of  $\beta$ -lactams as they can be cyclized to the latter compounds. Thus, we have carried out a model reaction to synthesise a key precursor for thienamycin type of compounds using  $\beta$ -keto amide **60**. Sodium borohydride reduction of **60c** provided a diastereomeric mixture of hydroxy amide **62** in quantitative yield. This type of compounds have already been converted to  $\beta$ -lactams<sup>19</sup> **63** which may be elaborated to thienamycin (Scheme 2.18). This preliminary result provides a potentially useful route to a wide range of  $\beta$ -lactams and our results seems superior to a similar palladium based methodology<sup>19</sup> for the synthesis of  $\beta$ -lactam. However, more experimental work is needed to really arrive at a definite conclusion on this route to  $\beta$ -lactams.

The reaction with ketones is more interesting than 1,3- dicarbonyl compounds. These

**Scheme 2.18**

reactions are faster than as compared with the reaction of 1,3-diketone. Interestingly, no enone formation was observed in these reactions. Thus the reaction with acetophenone **64** and propiophenone **66** provides a very high yields of  $\beta$ -keto amides **65** & **67** respectively as crystalline solids (Scheme 2.19). Once again there is no role of p-substitution on the formation

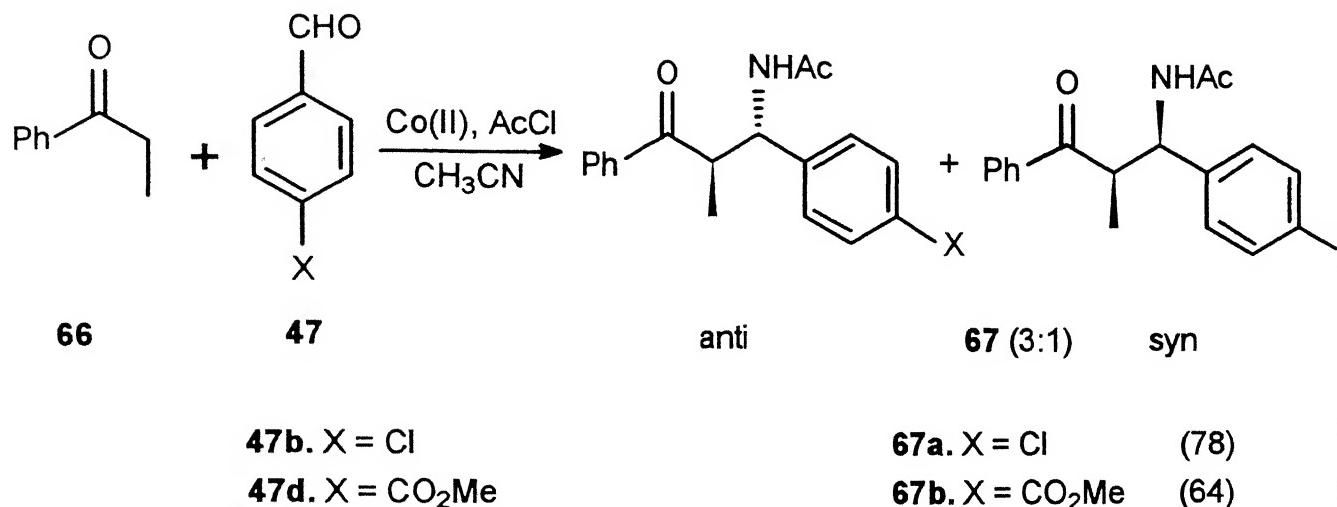


**47b.**  $\text{X} = \text{Cl}$   
**47c.**  $\text{X} = \text{NO}_2$   
**47d.**  $\text{X} = \text{CO}_2\text{Me}$

**65a.**  $\text{X} = \text{Cl}$  (64)  
**65b.**  $\text{X} = \text{NO}_2$  (56)  
**65c.**  $\text{X} = \text{CO}_2\text{Me}$  (59)

**Scheme 2.19**

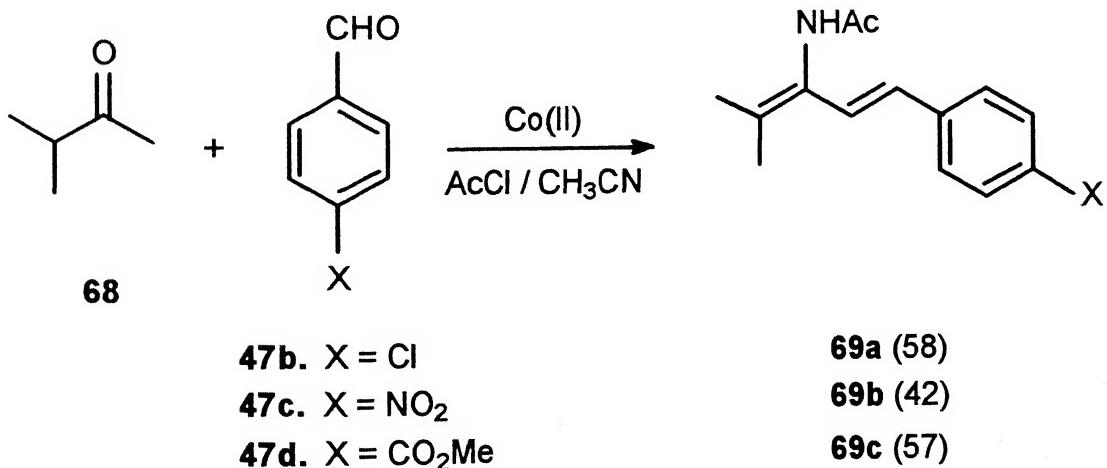
of these products. The reaction with propiophenone **66** gives a mixture of *syn* and *anti* diastereomers in a ratio of 1:3 (scheme 2.20). This methodology may be useful for the



**Scheme 2.20**

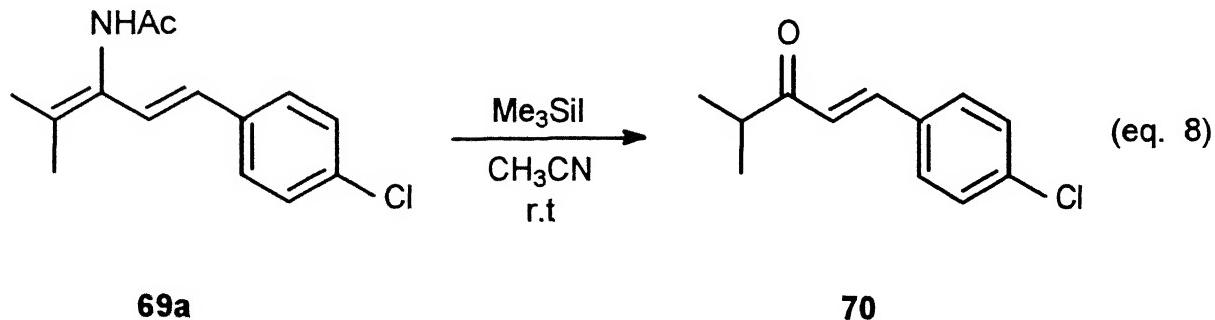
synthesis of 1,3-amino alcohols<sup>36</sup>, a key precursor for the synthesis of nikkomycin B<sup>37–39</sup>. The 1,3-amino alcohol can be obtained from the  $\beta$ -ketoamide on a simple stereoselective reduction

The reaction with aliphatic ketones are summarised in scheme 2.21. The reaction with isopropyl methyl ketone **68** gives the dienamides **69a-c** with p- substituted benzaldehydes

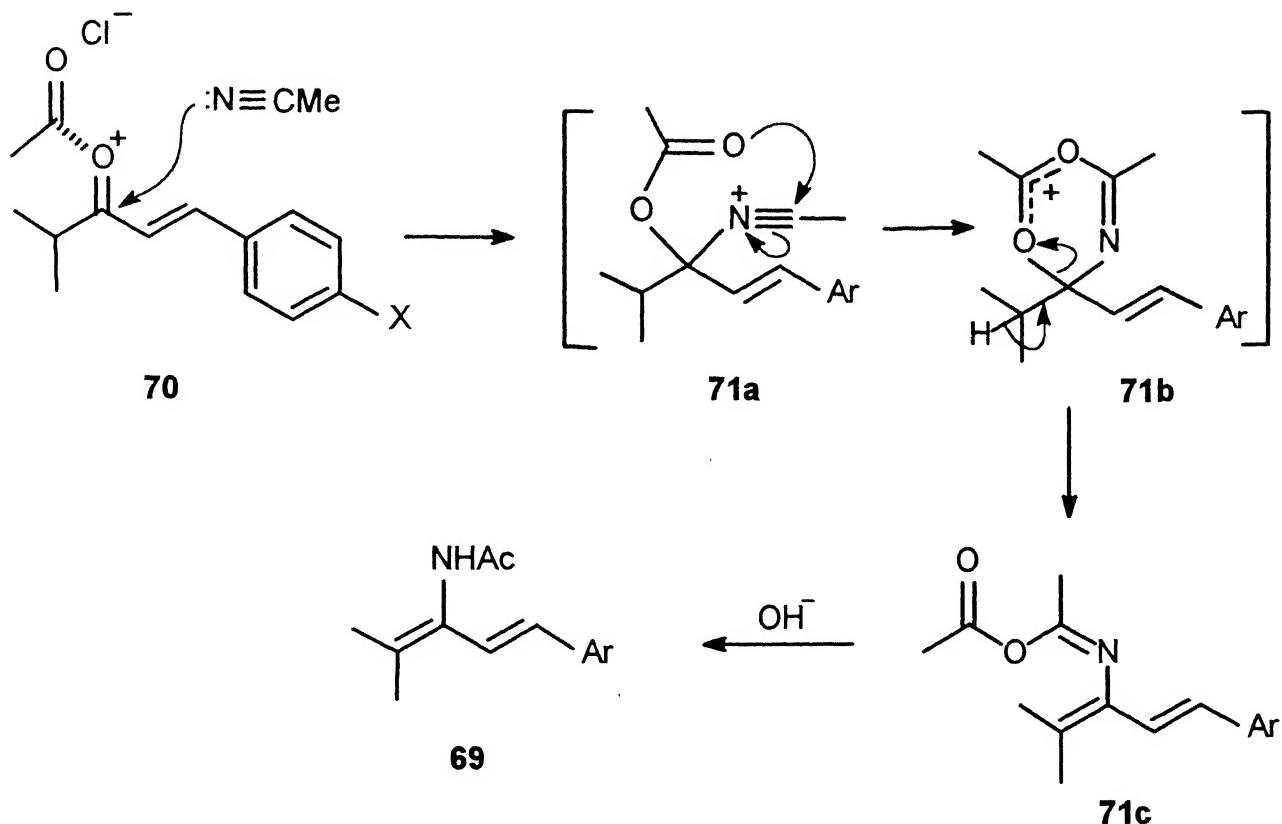


**Scheme 2.21**

**47b-d** in good yields. These results are rather surprising as no  $\beta$ -ketoamides are observed under these conditions. The geometry of the dienamide **69** was found to be trans based on the coupling constants of the olefinic protons in  $^1\text{H-NMR}$ . The structure for this compound was confirmed by trimethylsilyl iodide treatment of **69a** which gave the corresponding  $\alpha$ ,  $\beta$ -unsaturated ketone **70** as E-isomer (eq. 8). The hydrolysis of amides with trimethylsilyl iodide is very well presented in literature. The path way to the formation of dienamide

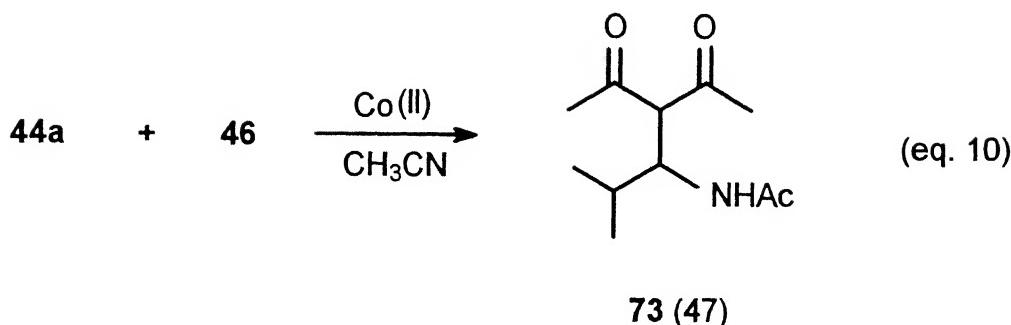
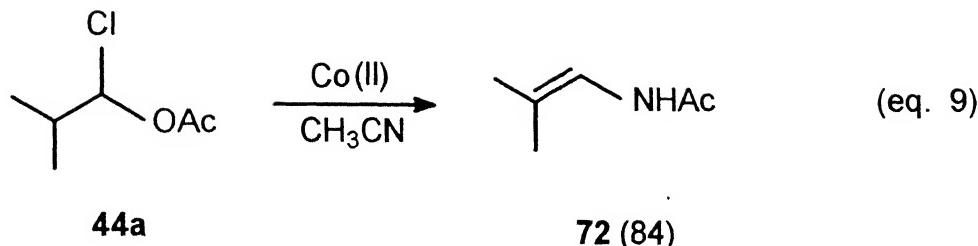


is not clear, however, it is possible that it is formed by an attack of acetonitrile on the initially formed enone **70** which is activated by the acetyl chloride. This will result into the formation of a cyclic dioxalane type intermediate **71b** which undergoes an intramolecular opening followed by the base hydrolysis to provide the dienamide **69** (Scheme 2.22).

**Scheme 2.22**

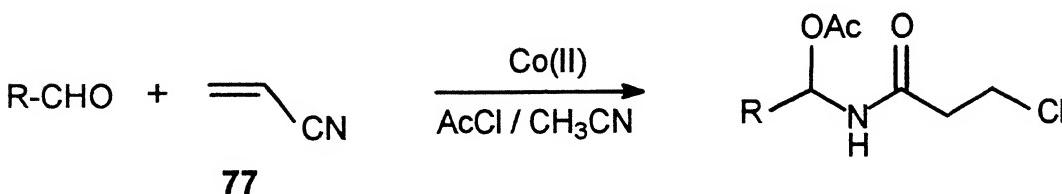
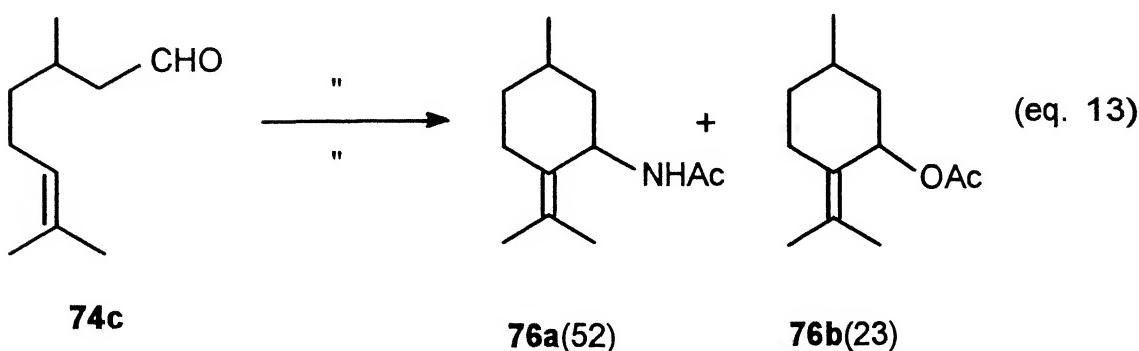
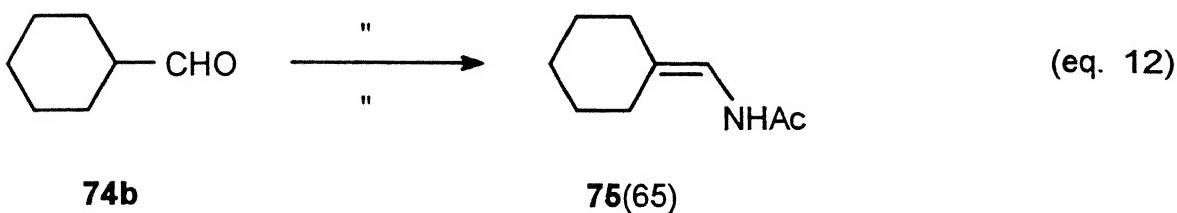
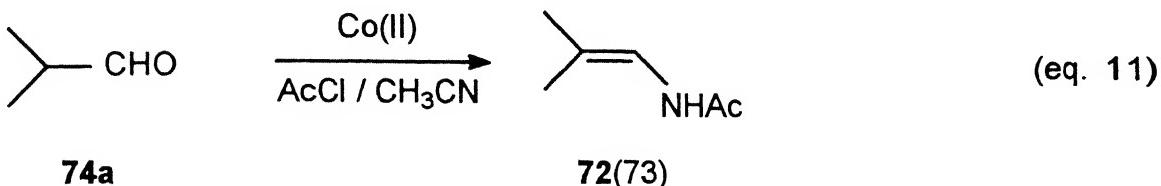
## MECHANISM

The mechanism of this reaction is not well understood at this moment, however, our preliminary investigation reveals that this reaction is proceeding via the initial cobalt(II) catalyzed formation of  $\alpha$ -chloroacetate from aldehyde and acetyl chloride. The  $\alpha$ -chloroacetate **44** from aliphatic aldehydes may be isolated as stable compounds whereas for the aromatic aldehydes this compound eludes separation and instead the corresponding  $\alpha$ -acetoxyamides **45** are obtained in quantitative yields. In the absence of carbonyl compound the  $\alpha$ -chloroacetate obtained from aliphatic aldehyde undergo amide formation on reaction with the acetonitrile (eq. 9). Amide **72** can be obtained from isobutyraldehyde without isolating the  $\alpha$ -chloroacetate. However, in the presence of 1,3-diketone **46** the  $\alpha$ -chloroacetate **44a** undergoes reaction to give the corresponding  $\beta$ -keto amide **73** (eq. 10). These observations clearly



indicate that  $\alpha$ -chloroacetate is the intermediate during the formation of  $\beta$ -ketoamides. In order to see the generality of this reaction we have carried out the reaction with different aliphatic aldehydes in the presence of cobalt chloride, acetonitrile and acetyl chloride. Thus isobutyraldehyde **74a** and cyclohexanecarboxaldehyde **74b** can be quantitatively converted into corresponding vinyl amides **72** and **75** respectively under these conditions (eq. 11, 12). The reaction with citronellal **74c** leads to a mixture of cyclized products **76a** & **76b** in which the cyclic amide **76a** was found to be the major product (eq. 13). Interestingly, acrylonitrile **77** can be used with different aliphatic aldehydes to provide  $\alpha$ -acetoxy ( $\beta$ -chloro propionyl) amide **78** as the only product in high yields. Surprisingly, no vinyl amide was observed under these conditions. These reactions clearly established that the initial product is  $\alpha$ -chloroacetate. However, in the case of acrylonitrile  $\alpha$ -chloroacetate could not be isolated. (Scheme 2.23).

Thus the cobalt catalyzed reaction of acetonitrile with  $\alpha$ - chloroacetate **44** may give a stabilized cationic species **79c** which will react with the cobalt enolate of ketone to afford the imidate ester **79d** and the latter on treatment with base during the workup may yield



74a R = <sup>i</sup>C<sub>3</sub>H<sub>7</sub>

78a(69)

**50a** R = <sup>n</sup>C<sub>3</sub>H<sub>7</sub>

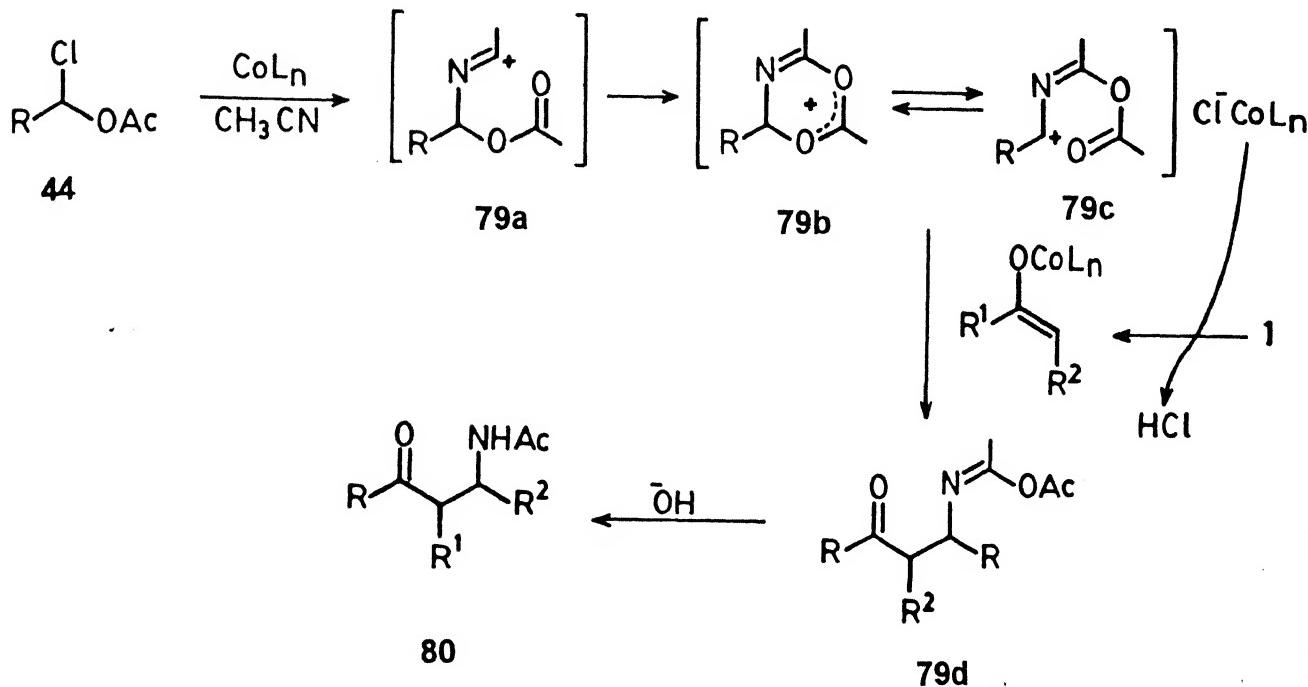
78b(64)

**74b** R = C<sub>2</sub>H<sub>5</sub>

78c(57)

### **Scheme 2.23**

the amide **80** (Scheme 2.24). Our recent studies have indicated that cobalt-enolates are formed during reaction of enolisable ketones with aldehyde or allylacetates. The high reactivity of ketones as compared with 1,3-dicarbonyl compounds also indicates that the reaction is proceeding via metal enolate as the stabilised enolate from the latter are likely to be less reactive than the corresponding enolate derived from ketones.

**Scheme 2.24**

In conclusion, this chapter has highlighted a novel route to  $\beta$ -keto amides by a one pot coupling of ketones, aldehydes and acetonitrile in the presence of catalytic amount of cobalt chloride and acetyl chloride. This unique approach to the access of  $\beta$ -keto amides has opened a new avenue for these biologically important organic molecules. We have also established in this chapter that cobalt(II) chloride is an efficient catalyst for the reaction between aldehydes and acetonitrile which has been unknown so far. The methodology described here will have wide applicability in the synthesis of a large number of compounds containing a hydroxy and an amino group in 1,3-position. The latter feature is fairly wide spread in large number of naturally occurring biologically active compounds. The mechanistic proposal presented here offers a plausible explanation of the formation of these compounds and the intermediacy of a stabilised cationic species is quite novel. Future endeavors in this project will concentrate on diastereoselectivity and the mechanistic aspects of these reactions.

## 2.3 EXPERIMENTAL

### Materials and Methods

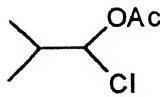
Acetonitrile, 1,2-dichloroethane, acetyl chloride were purified by the standard procedures. Cobalt(II) chloride was purchased from LOBA India Ltd., Bombay and dried at  $\sim 120^{\circ}\text{C}$  for 2-3 h prior to use. Column chromatography was performed by using ACME silica gel (60-120 mesh). Aldehydes, ketones, acetylacetone and methyl acetoacetate were purchased commercially and purified prior to use.  $^1\text{H-NMR}$  spectra were recorded at 60, 80 and 400 MHz in  $\text{CCl}_4$  or  $\text{CDCl}_3$ . The FAB Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer/Data System using Argon (6 KV, 10 mA) as the FAB gas.

Elemental analysis was conducted using Coleman automatic C, H and N analyzer. All the known compounds were characterised by comparing the data from the literature.

### General procedure for the preparation of $\alpha$ -chloroacetates

Aldehyde (10 mmol), acetyl chloride (20 mmol) and catalytic amount of  $\text{CoCl}_2$  ( $\sim 50$  mg) in 1,2-dichloroethane (30 mL) were stirred at room temperature for 10-15 h. Evaporation of the solvent gave a residue which was taken into ethyl acetate and washed with saturated sodium bicarbonate (4x30 mL), water (2x30 mL) and brine (1x25 mL). Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent gave the crude product which was purified by khugelrohr distillation.

**Compound 44a**

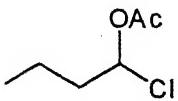


Isobutyraldehyde (2.88 g, 40 mmol), acetyl chloride (6.28 g, 80 mmol) and  $\text{CoCl}_2$  ( $\sim 100$  mg) in 1,2-dichloroethane (40 mL) were subjected to the reaction conditions as described above. The usual workup followed by distillation afforded 44a (5.54 g, 92%).

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  6.15 (d,  $J = 5.75$  Hz, 1H), 2.0 (s, 3H), 1.7-1.3 (m, 1H), 1.1 (d,  $J = 7.5$  Hz, 6H).

IR (Thinfilm) :  $\nu_{max}$  1730, 830 cm<sup>-1</sup>.

**Compound 44b**



Butyraldehyde (1.80 g, 25 mmol), acetyl chloride (3.92 g, 50 mmol) and CoCl<sub>2</sub> (~50 mg) in DCE (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by distillation afforded **44b** (3.27 g, 87%).

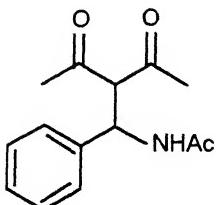
<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  6.15 (t, J = 7 Hz, 1H), 2.0 (s, 3H), 1.6-1.2 (m, 4H), 0.9 (t, J = 7.5 Hz, 3H).

IR (Thinfilm) :  $\nu_{max}$  1725, 830 cm<sup>-1</sup>.

### General Procedure for the Synthesis of $\beta$ -Ketoamides

Aldehyde (10 mmol), ketone or 1,3-diketone or -ketoester (10 mmol) and acetyl chloride (20 mmol) were added to a stirred solution of CoCl<sub>2</sub> (~30 mg) in dry acetonitrile (75 mL). The reaction mixture was stirred and heated at 85° C for 4-14 h. The solvent was evaporated in vacuo, and the residue was taken into ethyl acetate (75 mL) and the organic layer was washed successively with saturated sodium bicarbonate solution (4x25 mL), water (2x25 mL) and brine (1x30 mL). Drying (MgSO<sub>4</sub>) and evaporation of solvent gave the crude product which was purified by column chromatography (SiO<sub>2</sub>, 7:3 EtOAc, petroleum ether).

**Compound 48a**



Benzaldehyde **47a** (1.35 g, 12.5 mmol), acetylacetone **46** (1.5 g, 15 mmol), acetyl chloride

(1.96 g, 25 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) were taken in dry acetonitrile and the reaction was heated to  $85^{\circ}\text{C}$  for 12 h. The usual workup followed by chromatography afforded **48a** (1.5 g, 49%) as a solid, m.p.  $131\text{-}133^{\circ}\text{C}$ .

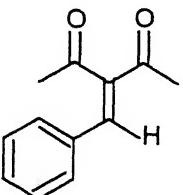
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.1 (s, 5H), 6.9 (br d, 1H), 5.6 (dd,  $J = 8.0$  Hz and  $5.0$  Hz, 1H), 4.05 (d,  $J = 6.0$  Hz, 1H), 2.0 (s, 3H), 1.8 (s, 3H), 1.7 (s, 3H).

IR (KBr) :  $\nu_{max}$  3280, 3080, 1720, 1700, 1650, 730,  $700\text{ cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_3$  : C, 68.03; H, 6.88.

Found : C, 68.17; H, 6.94.

Compound **49a**



This compound was separated from the reaction mixture as described for **49a** in 23% (0.53 g) yield.

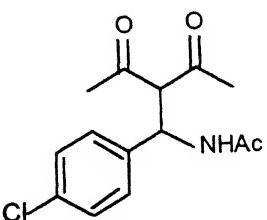
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.1 (s, 6H), 2.15 (s, 3H), 1.95 (s, 3H).

IR (Thinfilm) :  $\nu_{max}$  3080, 1690,  $1600\text{ cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{O}_2$  : C, 76.61; H, 6.38

Found : C, 76.68; H, 6.42.

Compound **48b**



4-Chloro benzaldehyde **47b** (0.9 g, 6.25 mmol), acetylacetone (0.65 g, 6.5 mmol), acetyl chloride (0.98 g, 12.5 mmol) and  $\text{CoCl}_2$  (50 mg) in dry acetonitrile (60 mL) were subjected to the reaction conditions as described above. The usual workup followed by purification by column chromatography yielded **48b** (0.96 g, 53%) as a solid, m.p.  $158^{\circ}\text{C}$ .

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.28 (s, 4H), 7.2-6.9 (m, 1H), 5.8 (dd, J = 10.0 and 6.0 Hz, 1H), 4.2 (d, J = 5.0 Hz, 1H), 2.25 (s, 3H), 2.1 (s, 3H), 2.0 (s, 3H).

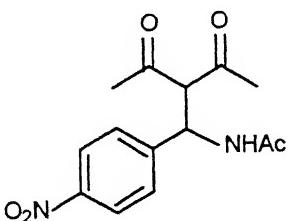
IR (KBr) : ν<sub>max</sub> 3300, 3080, 1720, 1700, 1650, 830 cm<sup>-1</sup>.

MS; m/z 282 (M<sup>+</sup>), 182 (BP), 140, 136, 43.

Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>ClNO<sub>3</sub> : C, 59.70; H, 5.68; N, 4.97.

Found : C, 59.82; H, 5.71; N, 5.08.

Compound 48c



4-Nitrobenzaldehyde **47c** (1.51 g, 10 mmol), acetylacetone (1.0 g, 10 mmol), acetyl chloride (1.57 g, 20 mmol) and CoCl<sub>2</sub> (~30 mg) were taken in dry acetonitrile (75 mL). The reaction mixture was stirred and heated at 85° C for 10 h. The usual workup followed by column chromatography afforded **48c** (1.4 g, 48%) as a solid, m.p. 171° C.

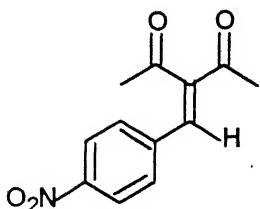
<sup>1</sup>H-NMR (DMSO-D6) : δ 8.2 (d, J = 10.0 Hz, 2H), 7.65 (d, J = 10.0 Hz, 2H), 5.9 (t, J = 8.75 Hz, 1H), 4.5 (d, J = 10.0 Hz, 1H), 2.22 (s, 3H), 2.12 (s, 3H), 2.0 (s, 3H).

IR (KBr) : ν<sub>max</sub> 3270, 3080, 1710, 1690, 1650, 1600, 850 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub> : C, 57.55; H, 5.48.

Found : C, 57.62; H, 5.54.

Compound 49b



This compound was separated from the reaction mixture as described for **48c** in 26% (0.60 g) yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 8.22 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.0 Hz, 3H), 2.44 (s, 3H), 2.2

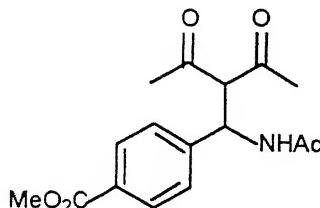
(s, 3H).

IR (KBr) :  $\nu_{max}$  3100, 1700, 1660, 1590  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{11}\text{NO}_4$  : C, 61.82; H, 4.72.

Found : C, 61.89; H, 4.76.

**Compound 48d**



Methyl 4-formylbenzoate **47d** (1.15 g, 7 mmol), acetylacetone (1.0 g, 10 mmol), acetyl chloride (1.1 g, 14 mmol) and  $\text{CoCl}_2$  (30 mg) were taken in dry acetonitrile and the reaction was stirred and heated at  $85^0 \text{ C}$  for 8h. The usual workup followed by column chromatography afforded **48d** (1.32 g, 62%) as a solid, m.p.  $150\text{-}151^0 \text{ C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  8.05 (d,  $J = 10.0 \text{ Hz}$ , 2H), 7.42 (d,  $J = 10.0 \text{ Hz}$ , 2H), 7.1 (br d, 1H), 5.95 (dd,  $J = 10.0$  and  $6.25 \text{ Hz}$ , 1H), 4.32 (d,  $J = 6.25 \text{ Hz}$ , 1H), 3.97 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H).

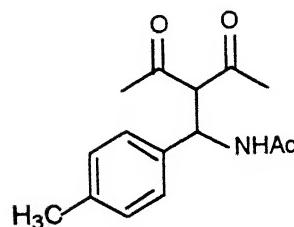
IR (KBr) :  $\nu_{max}$  3300, 1720, 1700, 1655, 1535, 1280, 770, 710  $\text{cm}^{-1}$ .

MS; m/z 306 (M $^+$ ), 220, 206 (BP), 164.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_5$  : C, 62.97; H, 6.22; N, 4.59.

Found : C, 63.04; H, 6.27; N, 4.64.

**Compound 48e**



p-Tolualdehyde **47e** (1.63 g, 13.5 mmol), acetylacetone (1.35 g, 13.5 mmol), acetyl chloride (2.13g, 27 mmol) and dry cobalt chloride (50 mg) were taken in dry acetonitrile (75 mL). The reaction mixture was stirred and heated at  $85^0 \text{ C}$  for 12 h. The usual workup followed

by column chromatography afforded **48e** (1.0 g, 29%) as a solid, m.p. 154<sup>0</sup> C.

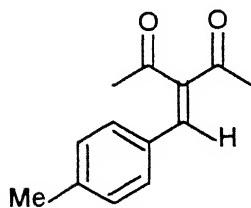
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.5-6.95 (m, 5H), 5.8 (dd, J = 10.0 and 6.25 Hz, 1H), 4.25 (d, J = 7.5 Hz, 1H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1 (s, 3H), 2.0 (s, 3H).

IR (KBr) : ν<sub>max</sub> 3310, 3060, 1715, 1695, 1640 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>3</sub> : C, 68.98; H, 7.27.

Found : C, 69.07; H, 7.35.

Compound **49c**



This compound was separated from the reaction mixture as described for **48e** in 23% (0.62 g) yield.

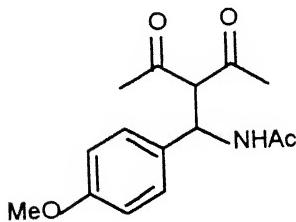
<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.15 (s, 1H), 7.0 (s, 4H), 2.35 (s, 3H), 2.25 (s, 3H), 2.1 (s, 3H).

IR (Thinfilm) : ν<sub>max</sub> 3080, 1700, 1600 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub> : C, 77.22; H, 6.93.

Found : C, 77.34; H, 6.97.

Compound **48f**



The reaction was performed as described above with p-anisaldehyde **47f** (1.36 g, 10 mmol), acetylacetone (1.0 g, 10 mmol) and acetyl chloride (1.57 g, 20 mmol) in the presence of catalytic amount of CoCl<sub>2</sub> (~30 mg) in dry acetonitrile (75 mL). Purification by column chromatography (SiO<sub>2</sub>) afforded **48f** (0.63 g, 23%) as a solid, m.p. 137-139<sup>0</sup> C.

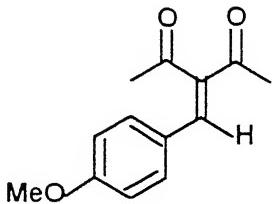
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.20 (d, J = 10.0 Hz, 2H), 6.85 (m, 3H), 5.80 (dd, J = 11.25 and 6.25 Hz, 1H), 4.28 (d, J = 7.5 Hz, 1H), 3.80 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H).

IR (KBr) :  $\nu_{max}$  3320, 3070, 1720, 1700, 1640, 840  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{15}\text{H}_{19}\text{NO}_4$  : C, 65.00; H, 6.85; N, 5.05.

Found : C, 65.08; H, 6.87; N, 5.13.

**Compound 49d**

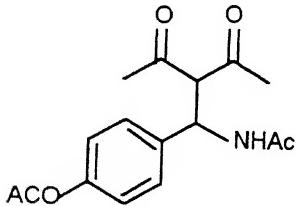


This compound was separated from the reaction mixture as described for **48f** in 53% (1.15 g) yield. M.P. 73 $^{\circ}$  C.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.1 (m, 3H), 6.65 (d,  $J = 10.0$  Hz, 2H), 3.75 (s, 3H), 2.25 (s, 3H), 2.2 (s, 3H).

IR ( $\text{CCl}_4$ ) :  $\nu_{max}$  3060, 1720, 1700, 1650, 1600  $\text{cm}^{-1}$ .

**Compound 48g**



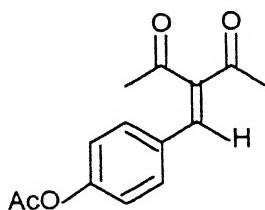
This compound was prepared as described above by the reaction of p-hydroxybenzaldehyde **47g** (1.22 g, 10 mmol), acetylacetone (1.0 g, 10 mmol), acetyl chloride (2.35 g, 30 mmol) and  $\text{CoCl}_2$  (~50 mg) in acetonitrile (100 mL) at 85 $^{\circ}$  C for 12 h to give **48g** (0.82 g, 27%), m.p. 134-136 $^{\circ}$  C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.2 (m, 4H), 5.9 (m, 1H), 4.28 (d,  $J = 6.25$  Hz, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 2.12 (s, 3H), 2.0 (s, 3H).

IR (KBr) :  $\nu_{max}$  3300, 3080, 1750, 1720, 1690, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_5$  : C, 62.97; H, 6.22.

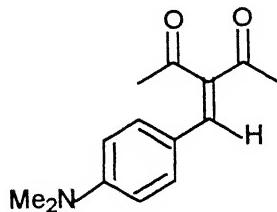
Found : C, 63.02; H, 6.27.

**Compound 49e**

This compound was isolated from the reaction mixture as described for **48g** in 54% (1.32 g) yield, m.p. 85<sup>0</sup> C.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.15 (m, 3H), 6.75 (m, 2H), 2.3 (s, 3H), 2.2 (s, 6H).

IR (KBr) : ν<sub>max</sub> 3080, 1750, 1700, 1640 cm<sup>-1</sup>.

**Compound 49f**

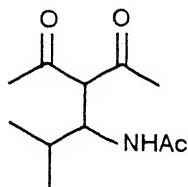
N,N-Dimethyl aminobenzaldehyde **47h** (0.93 g, 6.25 mmol), acetylacetone (0.75 g, 7.5 mmol), acetyl chloride (0.98 g, 12.5 mmol) and CoCl<sub>2</sub> (~30 mg) in acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **49f** (1.0 g, 69%) as a solid, m.p. 103<sup>0</sup> C.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.15 (d, J = 10.0 Hz, 3H), 6.5 (d, J = 10.0 Hz, 2H), 3.0 (s, 6H), 2.35 (s, 6H).

IR (KBr) : ν<sub>max</sub> 1690, 1630, 1570 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> : C, 72.74; H, 7.35.

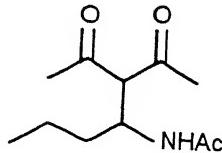
Found : C, 72.79; H, 7.39.

**Compound 73**

This compound was prepared by the reaction of **44a** (1.50 g, 10 mmol) with acetylacetone (1.0 g, 10 mmol) in the presence of  $\text{CoCl}_2$  ( $\sim$ 50 mg) in dry acetonitrile (75 mL) at  $85^\circ\text{C}$  for 8 h in 47% (0.7 g) yield.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  6.4 (br d, 1H), 4.2 (m, 1H), 3.85 (d,  $J = 5.0$  Hz, 1H), 2.2 (s, 3H), 2.05 (s, 3H), 1.80 (s, 3H), 0.85 (d,  $J = 7.5$  Hz, 6H).

IR ( $\text{CCl}_4$ ) :  $\nu_{max}$  3280, 3070, 1770, 1690, 1635  $\text{cm}^{-1}$ .

**Compound 51a**

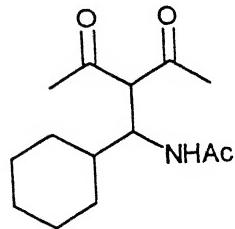
n-Butyraldehyde **50a** (0.72 g, 10 mmol), acetylacetone (1.0 g, 10 mmol), acetyl chloride (1.57 g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **51a** (0.55 g, 26%) as a solid, m.p.  $128^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  6.5 (br d, 1H), 4.68 (m, 1H), 3.92 (d,  $J = 5.0$  Hz, 1H), 2.32 (s, 3H), 2.18 (s, 3H), 2.0 (s, 3H), 1.4 (m, 4H), 0.8 (t,  $J = 5.0$  Hz, 3H).

IR (KBr) :  $\nu_{max}$  3300, 1710, 1695, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{19}\text{NO}_3$  : C, 61.99; H, 8.91.

Found : C, 62.12; H, 8.97.



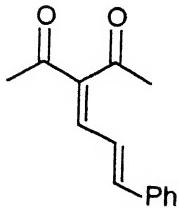
Cyclohexanecarboxaldehyde **50b** (1.12g, 10 mmol), acetylacetone (1.2g, 12 mmol) acetyl chloride (1.57 g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) were heated at  $80^\circ \text{C}$  in acetonitrile (75 mL) to afford **51b** (1.31 g, 52%) as a solid, m.p.  $144^\circ \text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  6.45 (br d, 1H), 4.53-4.2 (m, 1H), 4.0 (d,  $J = 5.0 \text{ Hz}$ , 1H), 2.25 (s, 3H), 2.1 (s, 3H), 1.87 (s, 3H), 1.78-1.31 (m, 5H), 1.19-0.87 (m, 6H).

IR (KBr) :  $\nu_{max}$  3250, 3070, 1700, 1650, 1560  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{23}\text{NO}_3$  : C, 66.42; H, 9.08; N, 5.53.

Found : C, 66.51; H, 9.14; N, 5.60.



Compound 53

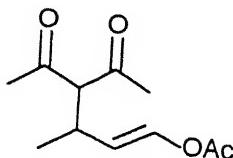
This compound was prepared from the reaction of cinnamaldehyde **52a** (0.8 g, 6 mmol), acetylacetone (0.73 g, 7.5 mmol), acetyl chloride (1.0 g, 12.5 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acetonitrile (75 mL) in 78% yield (1.01 g) as a solid, m.p.  $94^\circ \text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.5-6.9 (m, 8H), 2.43 (s, 6H).

IR (KBr) :  $\nu_{max}$  3060, 1690, 1640, 1610, 1580, 765, 700  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{O}_2$  : C, 78.52; H, 6.53.

Found : C, 78.63; H, 6.57.

**Compound 54**

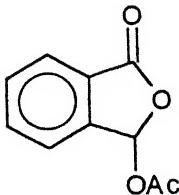
Crotonaldehyde **52b** (1.05g, 15 mmol), acetylacetone (1.50g, 15 mmol), acetyl chloride (2.35g, 30 mmol) and CoCl<sub>2</sub> (~30 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above for 10 h. The usual workup followed by column chromatography afforded **54** (2.16 g, 68% ).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.05 (d, J = 15 Hz, 1H), 5.2 (dd, J = 15 and 11 Hz, 1H), 3.5 (d, J = 12.5 Hz, 1H), 3.2-2.6 (m, 1H), 2.15 (s, 3H), 2.05 (s, 6H), 1.0 (d, J = 7.5 Hz, 3H).

IR (Thinfilm) : ν<sub>max</sub> 1755, 1700, 1365, 1220 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>11</sub>H<sub>16</sub>O<sub>4</sub> : C, 62.28; H, 7.54.

Found : C, 62.36; H, 7.58.

**Compound 56**

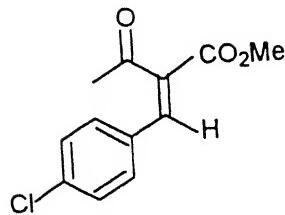
Phthalaldehydic acid **55** (1.5g, 10 mmol), acetylacetone (10g, 12 mmol), acetyl chloride (1.57g, 20 mmol) and CoCl<sub>2</sub> (~50 mg) were subjected to the reaction conditions as described above. The usual workup followed by crystallization afforded **56** (1.53g, 80%) as a solid, m.p. 61-62° C.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.9-7.5 (m, 4H), 7.3 (s, 1H), 2.2 (s, 3H).

IR (KBr) : ν<sub>max</sub> 1790, 1765 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>4</sub> : C, 62.52; H, 4.16.

Found : C, 62.64; H, 4.23.

**Compound 61a**

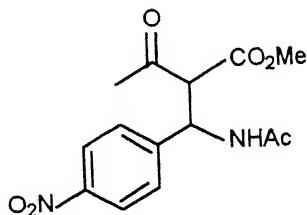
This compound was separated from the reaction mixture as described for **60a** in 12% (0.28g) yield. m.p.  $90^0 \text{ C}$ .

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.3 (s, 1H), 7.15 (s, 4H), 3.7 (s, 3H), 2.3 (s, 3H).

IR (KBr) :  $\nu_{max}$  3020, 1720, 1635, 1600, 1570  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{11}\text{ClO}_3$  : C, 60.40; H, 4.61.

Found : C, 60.49; H, 4.65.

**Compound 60b**

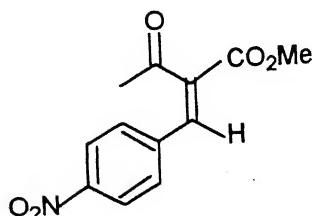
Aldehyde **47c** (1.51g, 10 mmol), methyl acetoacetate (1.39g, 12 mmol), acetyl chloride (1.57g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) were heated to  $80^0 \text{ C}$  in acetonitrile (75 mL) to afford **60b** (0.95g, 31%) as a solid, m.p.  $150\text{-}151^0 \text{ C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.95 (d,  $J = 10 \text{ Hz}$ , 2H), 7.3 (d,  $J = 10.0 \text{ Hz}$ , 3H), 5.65 (dd,  $J = 10.0$  and  $5.0 \text{ Hz}$ , 1H), 4.05 (d,  $J = 5.0 \text{ Hz}$ , 1H), 3.60 (s, 3H), 2.1 (s, 3H), 1.95 (s, 3H).

IR (KBr) :  $\nu_{max}$  3320, 3060, 1740, 1715, 1660  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6$  : C, 54.56; H, 5.19; N, 9.08.

Found : C, 54.71; H, 5.28; N, 9.17.

**Compound 61b**

This compound was separated from the reaction mixture as described for **60b** in 54%

(1.34g) yield. m.p. 134<sup>0</sup> C.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 8.3 (d, J = 10 Hz, 2H), 7.8 (m, 3H), 3.9 (s, 3H), 2.5 (s, 3H).

IR (KBr) : ν<sub>max</sub> 1720, 1640 cm<sup>-1</sup>.

Compound 60c



Methyl 4-formylbenzoate **47d** (1.15 g, 7 mmol), methyl acetoacetate (0.81 g, 7 mmol), acetyl chloride (1.09 g, 14 mmol) and CoCl<sub>2</sub> (~30 mg) were heated to 80<sup>0</sup> C in acetonitrile (75 mL) to afford **60c** (0.98 g, 44%). m.p. 126<sup>0</sup> C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 8.05 (d, J = 10.0 Hz, 2H), 7.43 (d, J = 10.0 Hz, 3H), 6.1-5.7 (m, 1H), 4.20 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.72 (s, 3H), 2.25 (s, 3H), 2.05 (s, 3H).

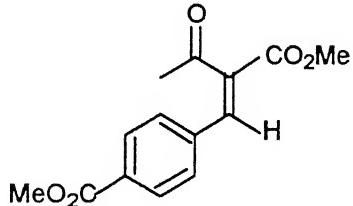
IR (KBr) : ν<sub>max</sub> 3350, 3080, 1740, 1720, 1640 cm<sup>-1</sup>.

MS; m/z 322 (M<sup>+</sup>), 206 (BP), 189, 164.

Anal. Calcd. for C<sub>16</sub>H<sub>19</sub>NO<sub>6</sub> : C, 59.83; H, 5.91; N, 4.36.

Found : C, 59.87; H, 5.96; N, 4.41.

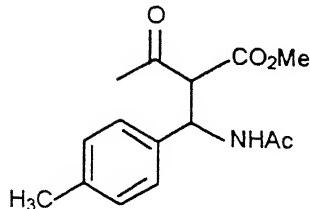
Compound 61c



This compound was separated from the reaction mixture as described for **60c** in 17% (0.31g) yield. M.P. 85<sup>0</sup> C.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.85 (d, J = 10 Hz, 2H), 7.4-7.1 (m, 3H), 3.8 (s, 3H), 3.7 (s, 3H), 2.35 (s, 3H).

IR (KBr) : ν<sub>max</sub> 1710, 1650, 1620 cm<sup>-1</sup>.

**Compound 60d**

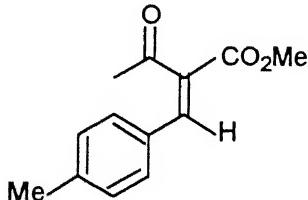
This reaction was performed as described with p-tolualdehyde **47e** (1.20 g, 10 mmol), methyl acetoacetate (1.16 g, 10 mmol), acetyl chloride (1.57 g, 20 mmol) and CoCl<sub>2</sub> (~50 mg) in acetonitrile. Purification by chromatography (SiO<sub>2</sub>) afforded **60d** (1.0 g, 36%) as a solid, m.p. 103-104° C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.6-6.95 (m, 5H), 5.8 (dd, J = 7.0 and 4.0 Hz, 1H), 4.05 (d, J = 5.0 Hz, 1H), 3.6 (s, 3H), 2.22 (s, 6H), 1.9 (m, 3H).

IR (KBr) : ν<sub>max</sub> 1720, 1650 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub> : C, 65.00; H, 6.85; N, 5.05.

Found : C, 65.12; H, 6.89; N, 5.17.

**Compound 61d**

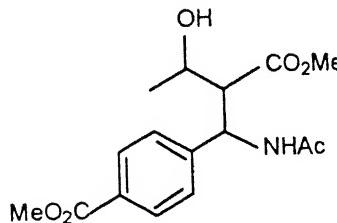
This compound was separated from the reaction mixture as described above for **60d** in 25% (0.54g) yield.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.15 (s, 1H), 7.0 (s, 4H), 3.9 (s, 3H), 2.3 (s, 3H), 2.15 (s, 3H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 1710, 1660, 1620 cm<sup>-1</sup>.

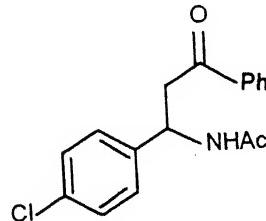
Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>3</sub> : C, 71.56, H, 6.42.

Found : C, 71.64; H, 6.48.

**Compound 62**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.93 (d, J = 8 Hz, 2H), 7.34 (m, 3H), 5.5 (t, J = 7.5 Hz, 1H), 4.2-3.85 (m, 2H), 3.81 (s, 3H), 3.5 (s, 3H), 2.75 (br s, 1H), 1.9 (s, 3H), 1.1 (d, J = 6.25 Hz, 3H).

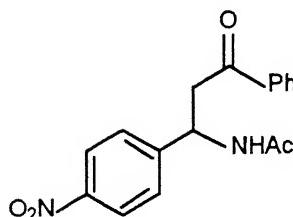
IR (CHCl<sub>3</sub>) : ν<sub>max</sub> 3400, 3300, 1720, 1650, 1280 cm<sup>-1</sup>.

**Compound 65a**

4-Chlorobenzaldehyde **47b** (1.40g, 10 mmol), acetophenone **64**(1.2g, 10 mmol), acetylene chloride (1.57g, 20 mmol) and CoCl<sub>2</sub> ( 30 mg) in dry acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by recrystallization (5:1 petroleum ether, methanol) afforded **65a** (1.93g, 64%) as a solid, m.p. 142-143° C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.95 (m, 2H), 7.5 (m, 2H), 7.37 (s, 5H), 6.87 (br d, 1H), 5.72-5.43 (m, 1H), 3.81 (dd, J = 17.5 and 5 Hz, 1H), 3.40 (dd, J = 17.5 and 5 Hz, 1H), 2.05 (s, 3H).

IR (KBr) : ν<sub>max</sub> 3280, 3080, 1690, 1650 cm<sup>-1</sup>.

**Compound 65b**

4-Nitrobenzaldehyde **47c** (1.51 g, 10 mmol), acetophenone (1.2 g, 10 mmol) acetyl chloride

(1.57 g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) were heated to  $80^\circ\text{C}$  for 5 h in acetonitrile (75 mL) to afford **65b** (1.74 g, 56%), m.p.  $139^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  8.05 (d,  $J = 9$  Hz, 2H), 7.86 (dd,  $J = 9$  and 2 Hz, 2H), 7.7-7.25 (m, 5H), 7.15 (br d, 1H), 5.60 (dt,  $J = 10.0$  and 2.5 Hz, 1H), 3.78 (dd,  $J = 17.5$  and 5 Hz, 1H), 3.06 (dd,  $J = 17.25$  and 5 Hz, 1H), 2.01 (s, 3H).

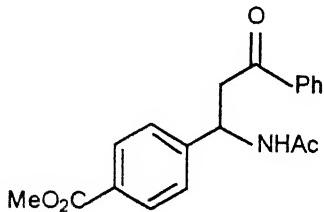
IR (KBr) :  $\nu_{max}$  3290, 1675, 1635, 1535, 1340, 850  $\text{cm}^{-1}$ .

MS; m/z 313 (M $^+$ ), 254, 151, 105 (BP).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$  : C, 65.40; H, 5.12; N, 8.97.

Found : C, 65.47; H, 5.16; N, 9.03.

Compound **65c**



Methyl 4-formyl benzoate **47d** (1.15 g, 7 mmol), acetophenone (0.84 g, 7 mmol), acetyl chloride (1.09 g, 14 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in dry acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography ( $\text{SiO}_2$ ) afforded **65c** (1.34 g, 59%) as a solid, m.p.  $178^\circ\text{C}$ .

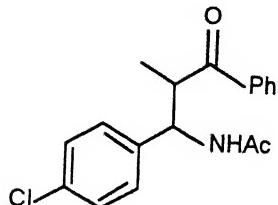
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  8.0 (m, 4H), 7.5 (m, 5H), 6.9 (br d, 1H), 5.6 (dt,  $J = 12.5$  and 5.0 Hz, 1H), 3.9 (s, 3H), 3.8 (dd,  $J = 17.5$  and 5.0 Hz, 1H), 3.4 (dd,  $J = 17.5$  and 5.0 Hz, 1H), 2.05 (s, 3H).

IR (KBr) :  $\nu_{max}$  3300, 3080, 1710, 1680, 1640  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{19}\text{H}_{19}\text{NO}_4$  : C, 70.17; H, 5.84; N, 4.30.

Found : C, 70.22; H, 5.89; N, 4.34.

Compound **67a**



4-Chlorobenzaldehyde **47b** (0.7 g, 5 mmol), propiophenone (0.67 g, 5 mmol), acetyl chlo-

ride (0.78 g, 10 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) were heated to  $80^\circ\text{C}$  in dry acetonitrile (75 mL) to afford **67a** (1.23g, 78%), m.p.  $164^\circ\text{C}$ .

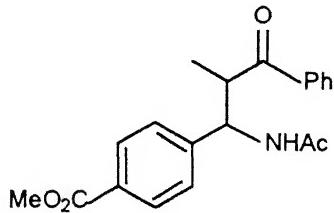
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.9 (d,  $J = 7.5$  Hz, 2H), 7.53 (d,  $J = 7.5$  Hz, 3H), 7.28 (s, 5H), 6.6 (br d, 1H), 5.47 (t,  $J = 8.75$  Hz, 1H), 4.1 (m, 1H), 2.05 (s, 3H), 1.3 (d,  $J = 7.5$  Hz, 3H).

IR (KBr) :  $\nu_{max}$  3260, 3050, 1660, 1630  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{18}\text{H}_{18}\text{ClNO}_2$  : C, 68.48; H, 5.70; N, 4.43.

Found : C, 68.53; H, 5.73; N, 4.49.

Compound **67b**



Methyl 4-formyl benzoate **47d** (0.82 g, 5 mmol), propiophenone (0.67 g, 5 mmol), acetyl chloride (0.78 g, 10 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in dry acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography ( $\text{SiO}_2$ ) afforded **67b** (1.08 g, 64%) as a solid, m.p.  $138^\circ\text{C}$ .

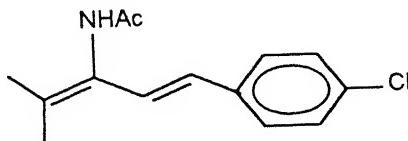
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.90 (d,  $J = 8.5$  Hz, 2H), 7.78 (dd,  $J = 8.5$  and 2 Hz, 2H), 7.35-7.10 (m, 5H), 5.31 (dd,  $J = 10.0$  and 5 Hz, 1H), 4.15 (m, 1H), 3.81 (s, 3H), 2.05 (s, 3H), 1.32 (d,  $J = 7.5$  Hz, 3H).

IR (KBr) :  $\nu_{max}$  3300, 3080, 1720, 1680, 1650  $\text{cm}^{-1}$ .

MS; m/z 340 (M $^+$ ), 206 (BP), 164, 105.

Anal. Calcd. for  $\text{C}_{20}\text{H}_{21}\text{NO}_4$  : C, 70.81; H, 6.19; N, 4.12

Found : C, 70.87; H, 6.23; N, 4.15.

**Compound 69a**

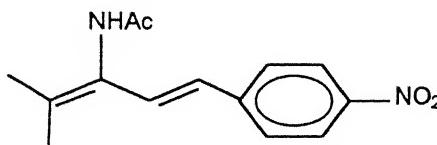
4-Chloro benzaldehyde **47b** (1.4 g, 10 mmol), 3-methyl 2-butanone **68** (1.03 g, 10 mmol), acetyl chloride (1.57 g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) were heated to  $80^\circ\text{C}$  in acetonitrile (75 mL) to afford **69a** (1.5 g,  $58^1\text{H-NMR}$  (400 MHz, DMSO-D6) :  $\delta$  8.75 (s, 1H), 7.55 (d,  $J = 1.6$  Hz, 2H), 7.35 (d,  $J = 1.6$  Hz, 2H), 7.2 (d,  $J = 3.75$  Hz, 1H), 6.4 (d,  $J = 3.75$  Hz, 1H), 2.0 (s, 3H), 1.95 (s, 3H), 1.7 (s, 3H).

IR (KBr) :  $\nu_{max}$  3260, 1660, 1635  $\text{cm}^{-1}$ .

MS ; M/Z 250 (BP), 249, 208, 156, 124, 77.

Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{ClNO}$  : C, 67.35; H, 6.41; N, 5.61.

Found : C, 67.39; H, 6.47; N, 5.69.

**Compound 69b**

This compound was prepared from the reaction of 4-nitrobenzaldehyde **47c** (1.51 g, 10 mmol), 3-methyl-2-butanone (1.03 g, 12 mmol), acetyl chloride (1.57 g, 20 mmol) and  $\text{CoCl}_2$  (50 mg) in dry acetonitrile (75 mL) in 42% (1.16 g) yield as a solid, m.p.  $202\text{-}204^\circ\text{C}$ .

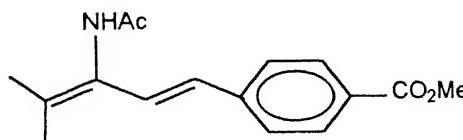
$^1\text{H-NMR}$  (400 MHz, DMSO-D6) :  $\delta$  8.8 (s, 1H), 7.9 (d,  $J = 1.6$  Hz, 2H), 7.65 (d,  $J = 1.6$  Hz, 2H), 7.35 (d,  $J = 3.75$  Hz, 1H), 6.5 (d,  $J = 3.75$  Hz, 1H), 2.0 (s, 3H), 1.9 (s, 3H), 1.7 (s, 3H).

IR (KBr) :  $\nu_{max}$  3260, 1650  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$  : C, 64.63; H, 6.15; N, 10.76

Found : C, 64.76; H, 6.19; N, 10.79.

**Compound 69c**



Methyl 4-formyl benzoate **47d** (0.82 g, 5 mmol), 3-methyl 2-butanone (0.60 g, 7 mmol), acetyl chloride (0.78 g, 10 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in acetonitrile (75 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **69c** (0.83 g, 57%) as a solid, m.p.  $165\text{-}166^{\circ}\text{C}$ .

$^1\text{H-NMR}$  (400 MHz, DMSO-D6) :  $\delta$  8.8 (s, 1H), 7.9 (d,  $J = 1.6$  Hz, 2H), 7.65 (d,  $J = 1.6$  Hz, 2H), 7.35 (d,  $J = 3.75$  Hz, 1H), 6.45 (d,  $J = 3.75$  Hz, 1H), 3.85 (s, 3H), 2.0 (s, 3H), 1.95 (s, 3H), 1.7 (s, 3H).

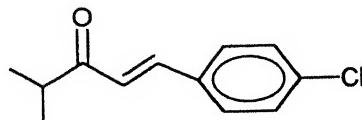
IR (KBr) :  $\nu_{max}$  3260, 1720, 1640  $\text{cm}^{-1}$ .

MS ; M/Z 274 (BP), 242, 232, 154, 124.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_3$  : C, 70.34; H, 6.95; N, 5.12.

Found : C, 70.52; H, 6.99; N, 5.19.

**Compound 70**



Sodium iodide (0.38g, 2.53 mmol) was taken in dry acetonitrile (30 mL). Chlorotrimethylsilane (0.26g, 2.4 mmol) was added at  $0^{\circ}\text{C}$  and the reaction mixture was stirred for 0.5h. Then  $\text{CoCl}_2$  ( $\sim$ 30 mg) and compound **69a** (0.53g, 2 mmol) were added and stirred at room temperature for 18h. Solvent was evaporated on vacuo, the residue was taken into ethylacetate. The usual workup followed by column chromatography afforded **70** (0.30g, 72%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.6 (d,  $J = 8.75$  Hz, 1H), 7.4 (d,  $J = 5$  Hz, 4H), 6.75 (d,  $J = 16.25$  Hz,

1H), 2.9 (sep,  $J = 7.5$  Hz, 1H), 1.1 (d,  $J = 7.5$  Hz, 6H).

IR ( $\text{CHCl}_3$ ) :  $\nu_{max}$  1680, 1600, 1380, 1250  $\text{cm}^{-1}$ .

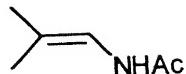
Anal. Calcd. for  $\text{C}_{12}\text{H}_{13}\text{ClO}$  : C, 69.08; H, 6.23.

Found : C, 69.17; H, 6.26.

### General Procedure for the Preparation of Vinyl Amides

Aldehyde (10 mmol), acetyl chloride (20 mmol) and catalytic amount of  $\text{CoCl}_2$  ( $\sim 30$  mg) in dry acetonitrile (50 mL) were stirred at room temperature for 8-10h. The solvent was evaporated on vacuo, the residue was taken into ethyl acetate and washed with saturated sodium bicarbonate (4x30 mL), water (2x30 mL) and brine (1x25 mL). Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent gave the crude product which was purified by column chromatography ( $\text{SiO}_2$ , 7:3 ethylacetate, petroleum ether).

Compound 72



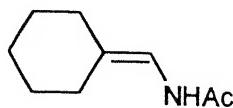
Isobutyraldehyde **74a** (0.72g, 10 mmol), acetyl chloride (1.57g, 20 mmol) and  $\text{CoCl}_2$  ( $\sim 30$  mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **72** (0.82g, 73%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  8.7 (br d, 1H), 6.5 (br d, 1H), 2.0 (s, 3H), 1.65 (s, 6H).

IR ( $\text{CHCl}_3$ ) :  $\nu_{max}$  3300, 3040, 1650  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_6\text{H}_{10}\text{NO}$  : C, 63.73; H, 9.73.

Found : C, 63.82; H, 9.77.

**Compound 75**

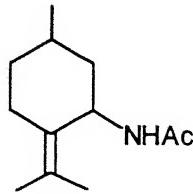
This compound was prepared from the reaction of cyclohexanecarboxaldehyde **74b** (1.12g, 10 mmol), acetyl chloride (1.5g, 20 mmol) and CoCl<sub>2</sub> (~30 mg) in dry acetonitrile (50 mL) in 65% (1.0g) yield as a solid, m.p. 91-92° C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.44 (br d, 1H), 6.47 (d, J = 12.5 Hz, 1H), 2.0 (m, 7H), 1.55 (s, 6H).

IR (KBr) : ν<sub>max</sub> 3290, 3024, 1650, 1530 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>10</sub>H<sub>16</sub>NO : C, 70.60; H, 9.80.

Found : C, 70.65; H, 9.83.

**Compound 76a**

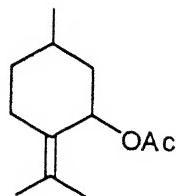
This reaction was performed as described above with citronellal **74c** (1.54g, 10 mmol), acetylchloride (1.57g, 20 mmol) and CoCl<sub>2</sub> (~30 mg) in acetonitrile. Purification by column chromatography afforded **76a** (1.01g, 52%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.1 (br d, 1H), 4.15 (m, 1H), 1.8 (s, 3H), 1.7-0.8 (m, 16H).

IR (CHCl<sub>3</sub>) : ν<sub>max</sub> 3320, 1660, 1530, 1450, 1370 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>21</sub>NO : C, 73.86; H, 10.76.

Found : C, 73.95; H, 10.80.

**Compound 76b**

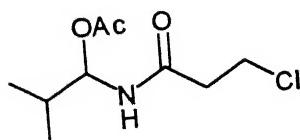
This compound was separated from the reaction mixture as described for **76a** in 23% (0.45g) yield.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 5.25 (m, 1H), 2.0 (s, 3H), 1.9-1.7 (m, 2H), 1.65-1.2 (m, 11H), 1.0 (m, 3H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 1720, 1450, 1360, 1230 cm<sup>-1</sup>.

#### General Procedure for the synthesis of α-acetoxy, (β-Chloropropionyl) amide.

Aldehyde (10 mmol), acetyl chloride (10 mmol), acrylonitrile (30 mmol) and catalytic amount of CoCl<sub>2</sub> (~30 mg) in 1,2-dichloroethane (30 mL) were stirred at room temperature for 18-24h. Removal of solvent gave a residue which was taken into ethyl acetate and washed with saturated sodium bicarbonate (4x25 mL), water (2x25 mL) and brine (1x25 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation of the solvent gave the product as thick liquid.

**Compound 78a**

Isobutyraldehyde **74a** (0.72g, 10 mmol), acetyl chloride (0.78g, 10 mmol), acrylonitrile (1.59g, 30 mmol) and CoCl<sub>2</sub> (~30 mg) in 1,2-dichloroethane were subjected to the reaction conditions as described above. The usual workup afforded **78a** (1.53g, 69%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.2 (br d, 1H), 6.05 (d, J = 5.75 Hz, 1H), 3.6 (t, J = 7.5 Hz, 2H), 2.8 (t,

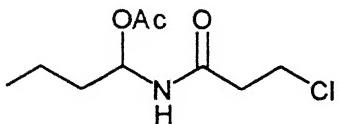
$J = 7.5$  Hz, 2H), 2.0 (s, 3H), 1.7-1.3 (m, 1H), 1.0 (d,  $J = 7.5$  Hz, 6H).

IR (Thinfilm) :  $\nu_{max}$  3280, 1710, 1650, 820  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_9\text{H}_{16}\text{ClNO}_3$  : C, 48.78; H, 7.22.

Found : C, 48.91; H, 7.25.

Compound 78b

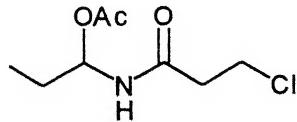


This compound was prepared from the reaction of butyraldehyde **50a** (1.08g, 15 mmol), acetyl chloride (1.18g, 15 mmol), acrylonitrile (2.39g, 45 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in DCE (30 mL) in 64% (2.12g) yield.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.15 (br d, 1H), 6.15 (t,  $J = 6.5$  Hz, 1H), 3.6 (t,  $J = 7.5$  Hz, 2H), 2.7 (t,  $J = 7.5$  Hz, 2H), 2.0 (s, 3H), 1.6-1.0 (m, 4H), 0.8 (t,  $J = 7.0$  Hz, 3H).

IR ( $\text{CCl}_4$ ) :  $\nu_{max}$  3300, 1715, 1650, 820  $\text{cm}^{-1}$ .

Compound 78c



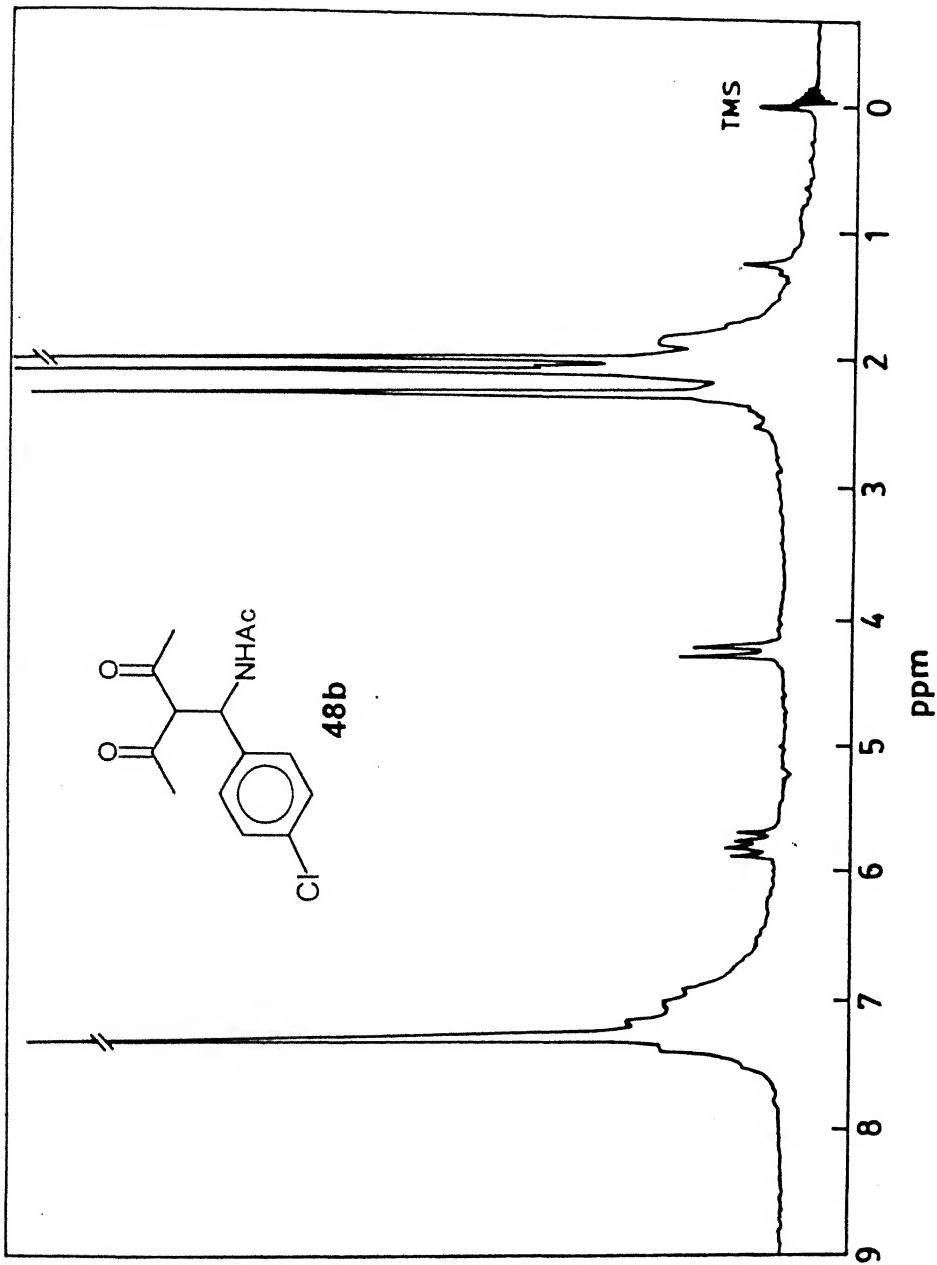
Propionaldehyde **74d** (0.87g, 15 mmol), acetyl chloride (1.18g, 15 mmol), acrylonitrile (2.39g, 45 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in DCE (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **78c** in 57% (1.77g) yield.

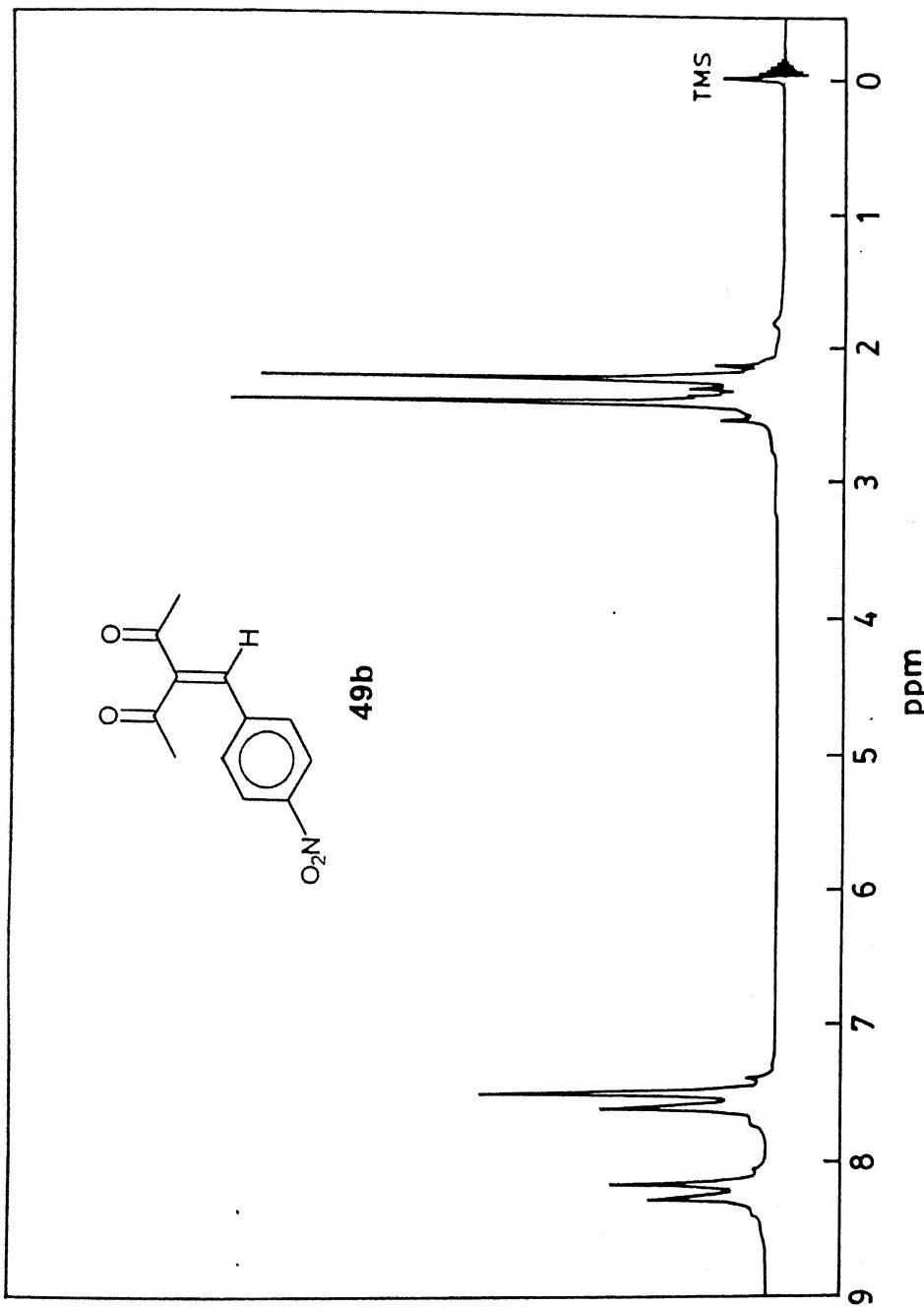
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  6.4 (t,  $J = 5.75$  Hz, 2H), 3.65 (t,  $J = 7.5$  Hz, 2H), 2.7 (t,  $J = 7.5$  Hz, 2H), 2.0 (s, 3H), 1.9-1.5 (m, 2H), 1.2-0.8 (m, 3H).

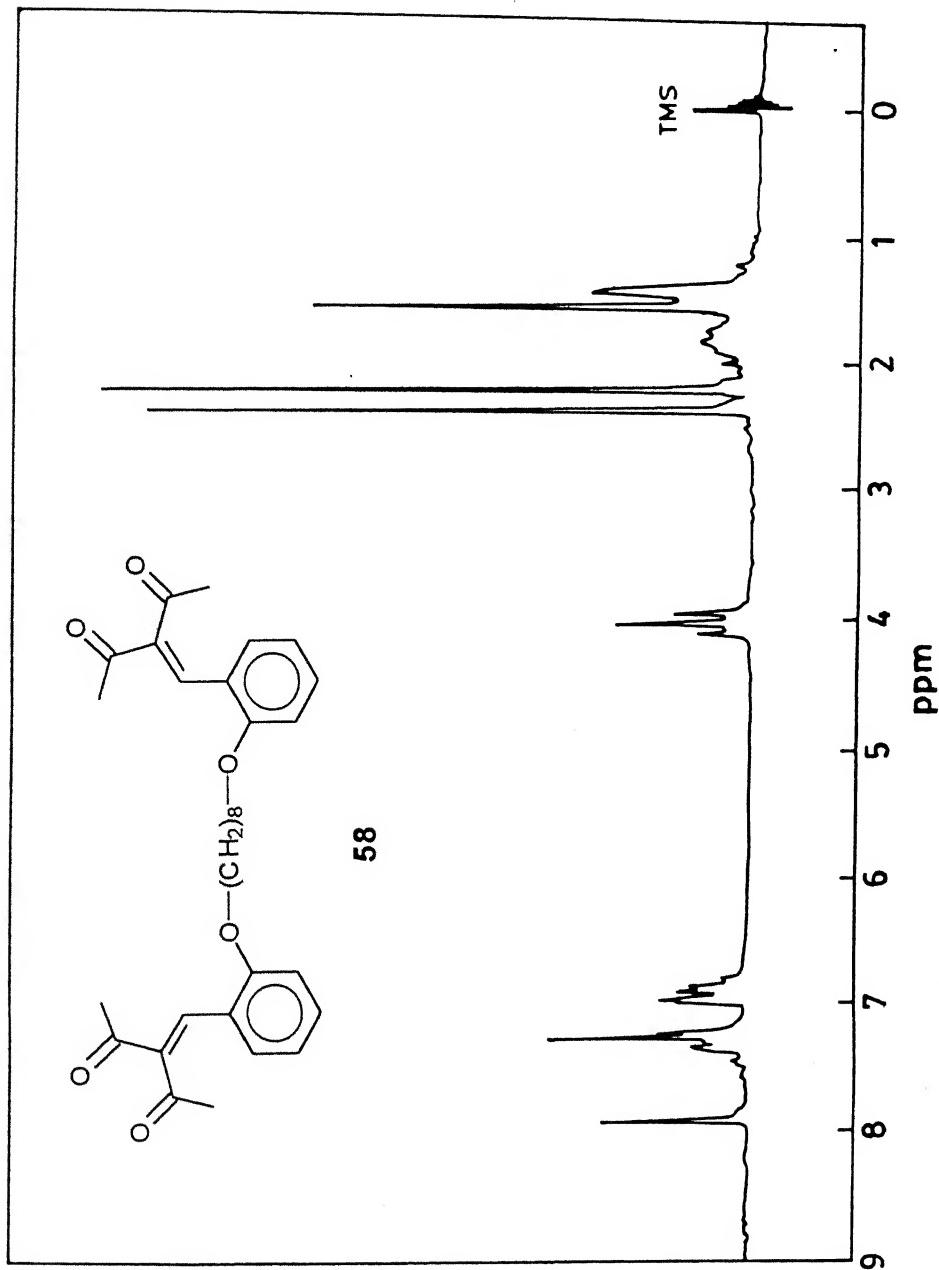
IR (Thinfilm) :  $\nu_{max}$  3280, 1710, 1640, 820  $\text{cm}^{-1}$ .

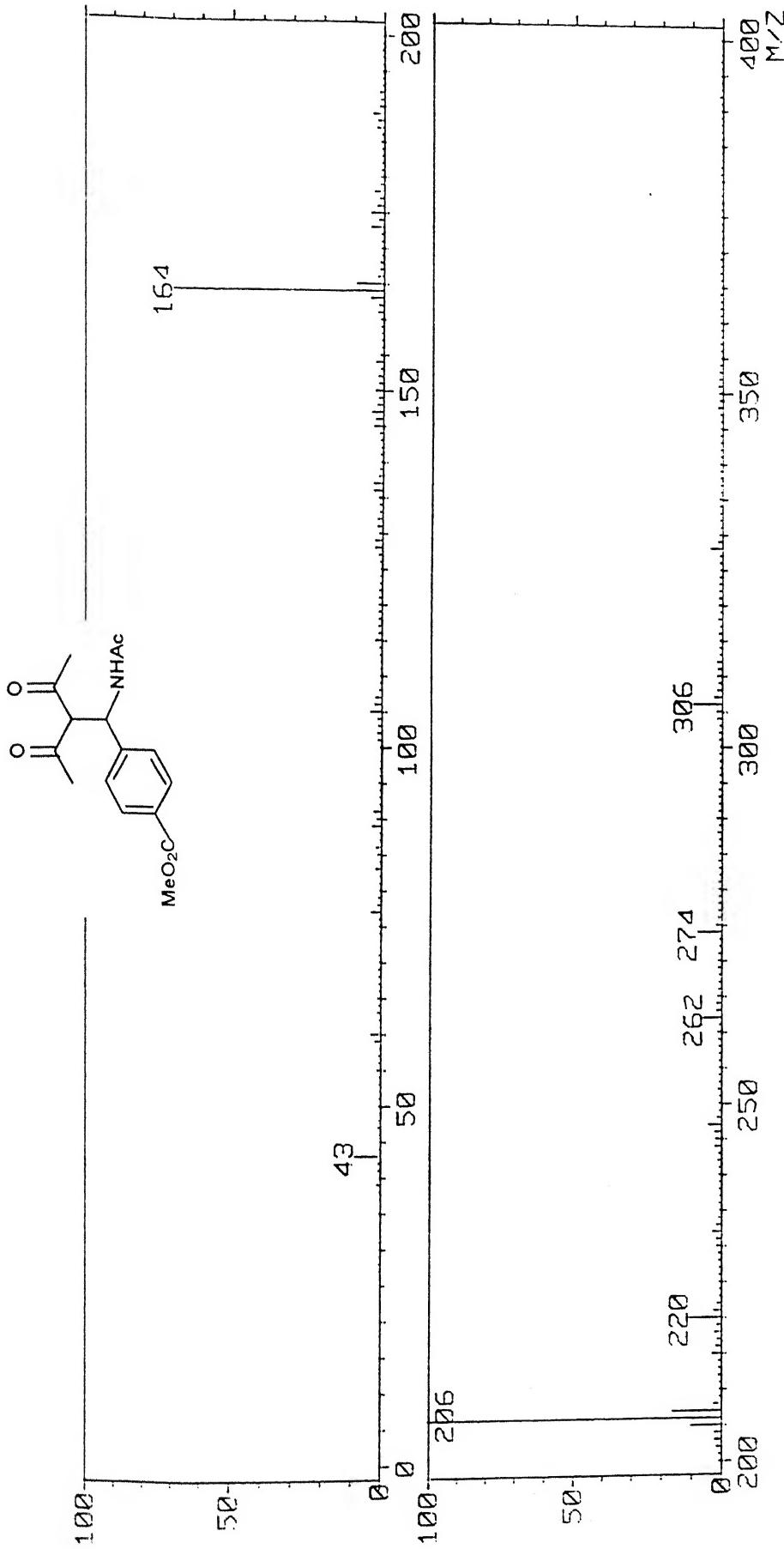
Anal. Calcd. for  $\text{C}_8\text{H}_{14}\text{ClNO}_3$  : C, 46.28; H, 6.74.

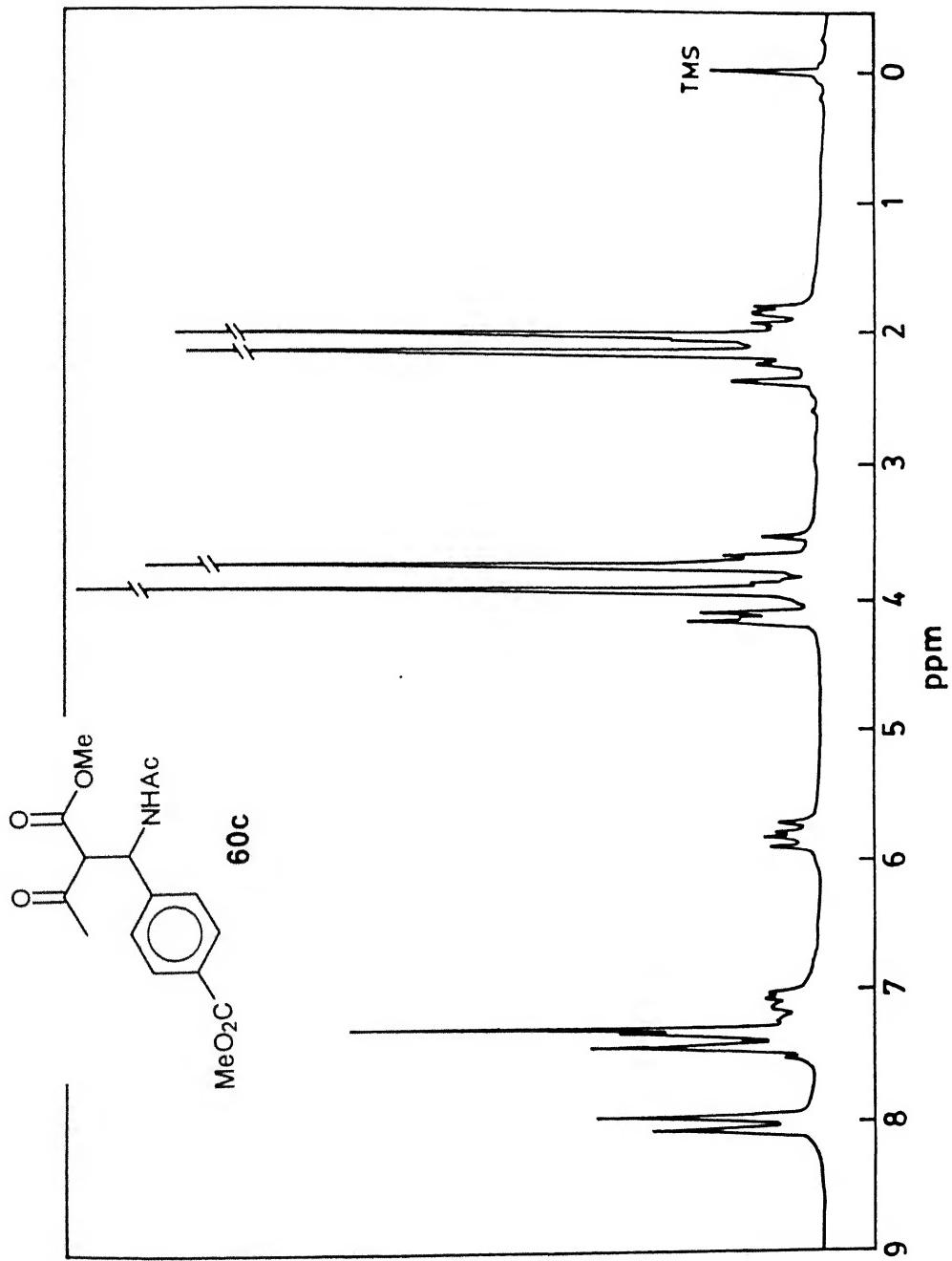
Found : C, 46.39; H, 6.77.

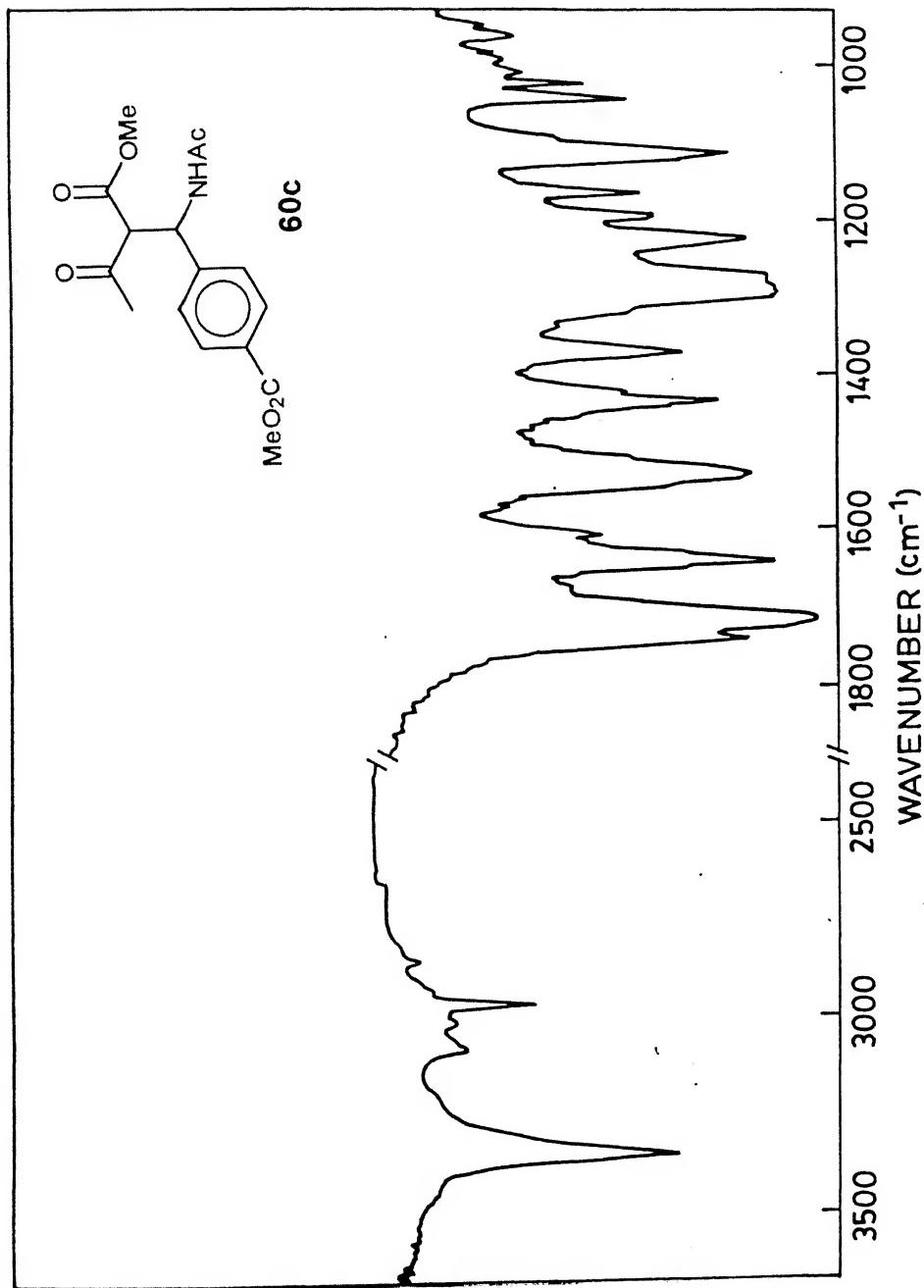


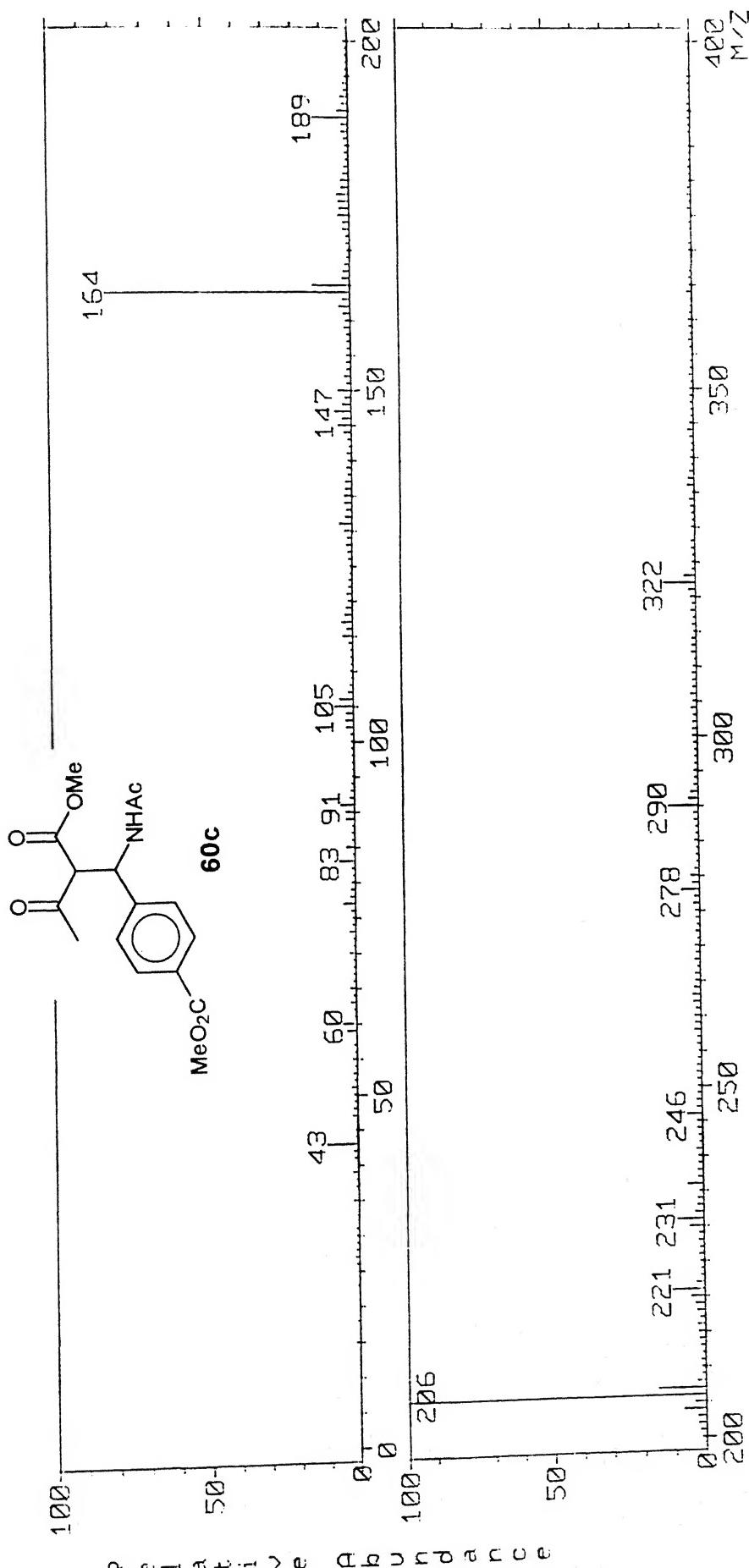


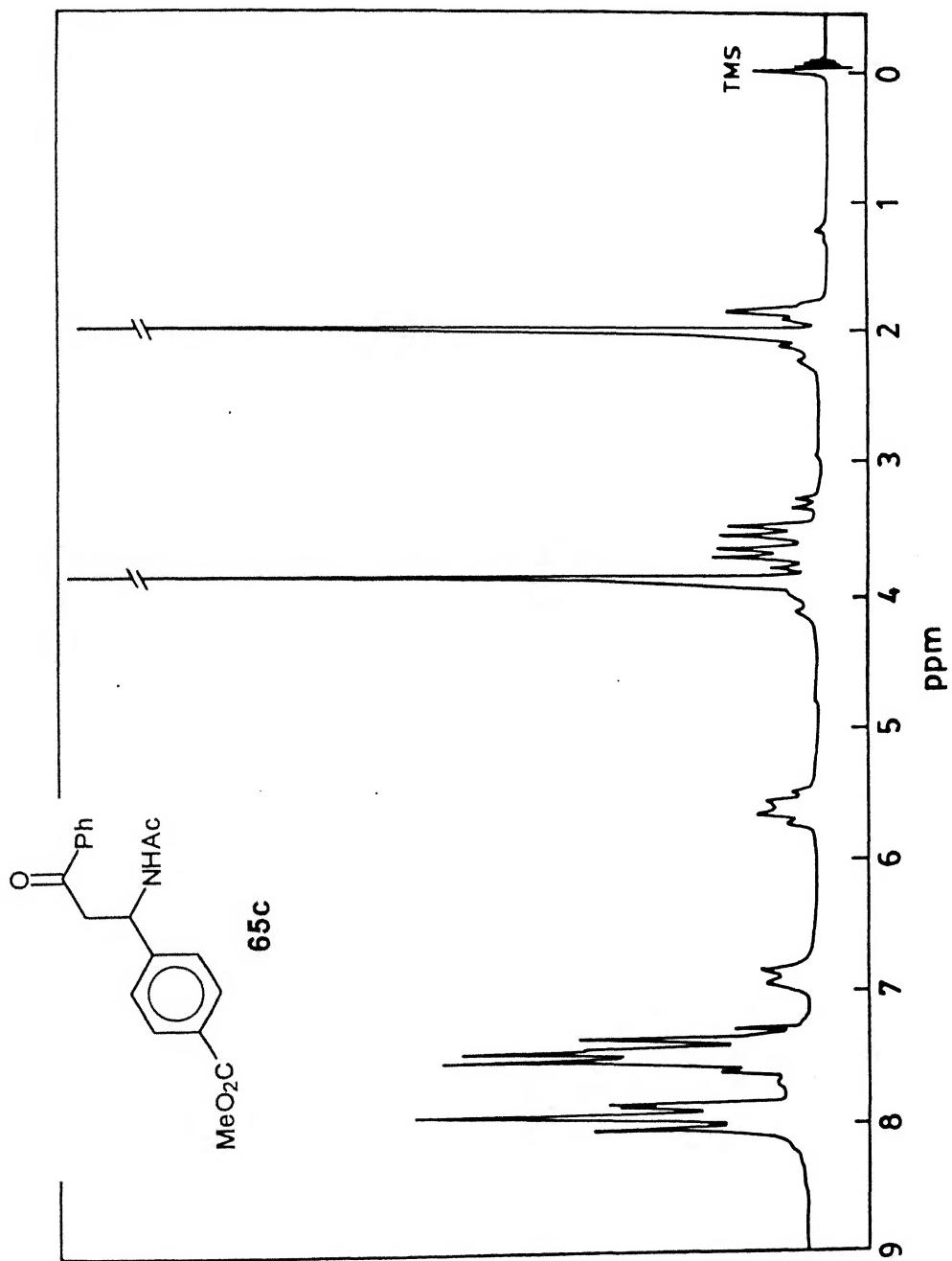


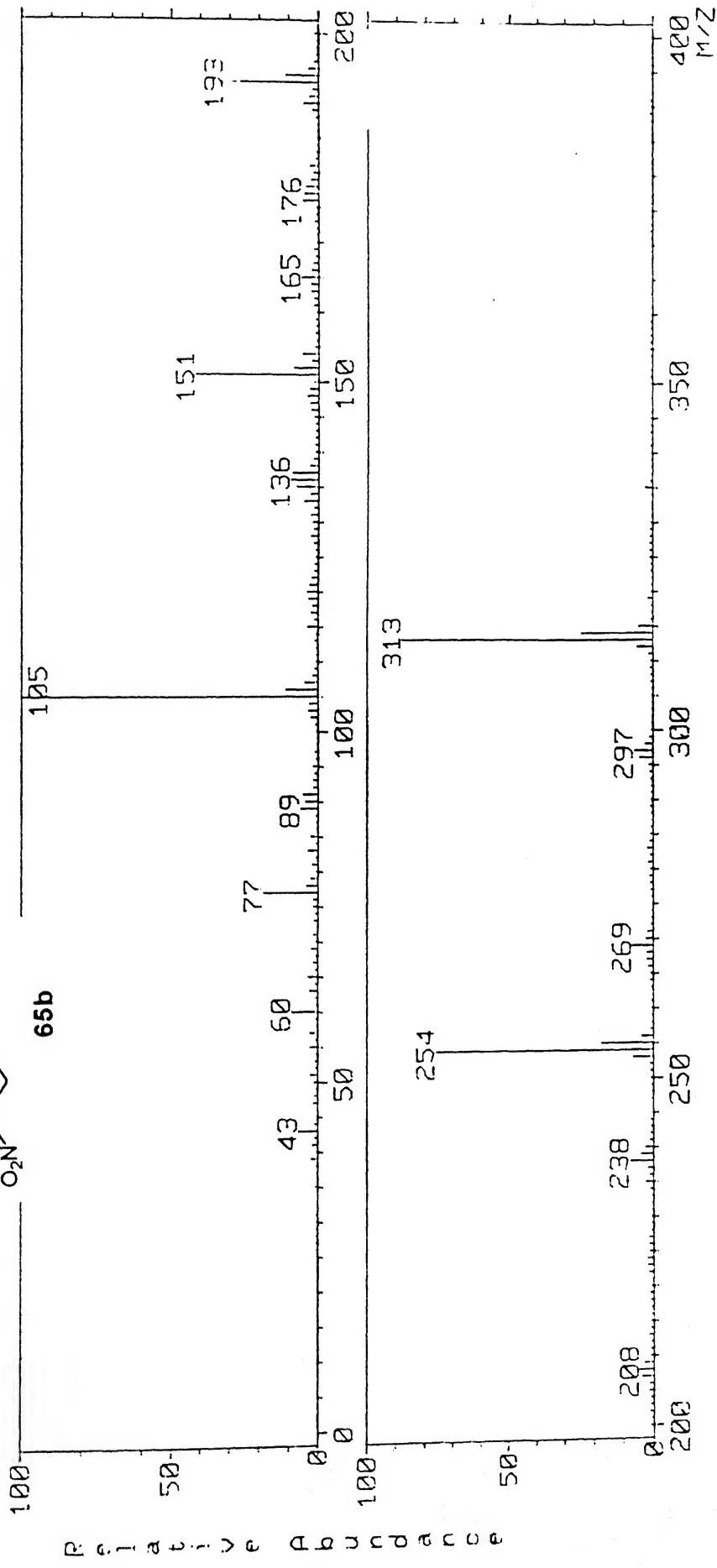
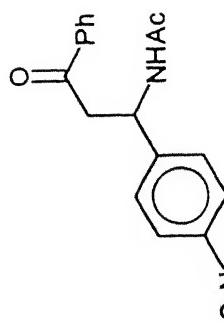


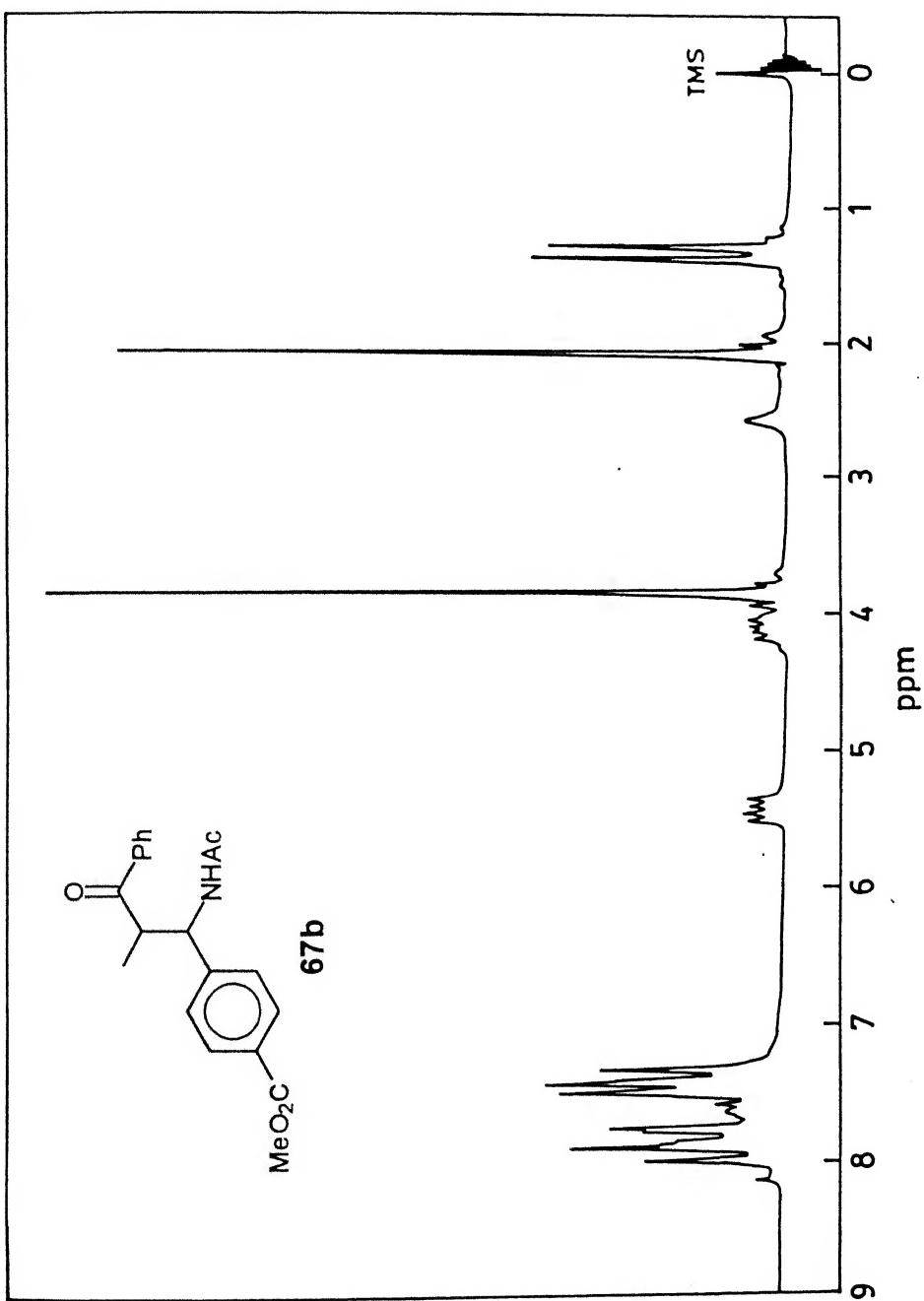


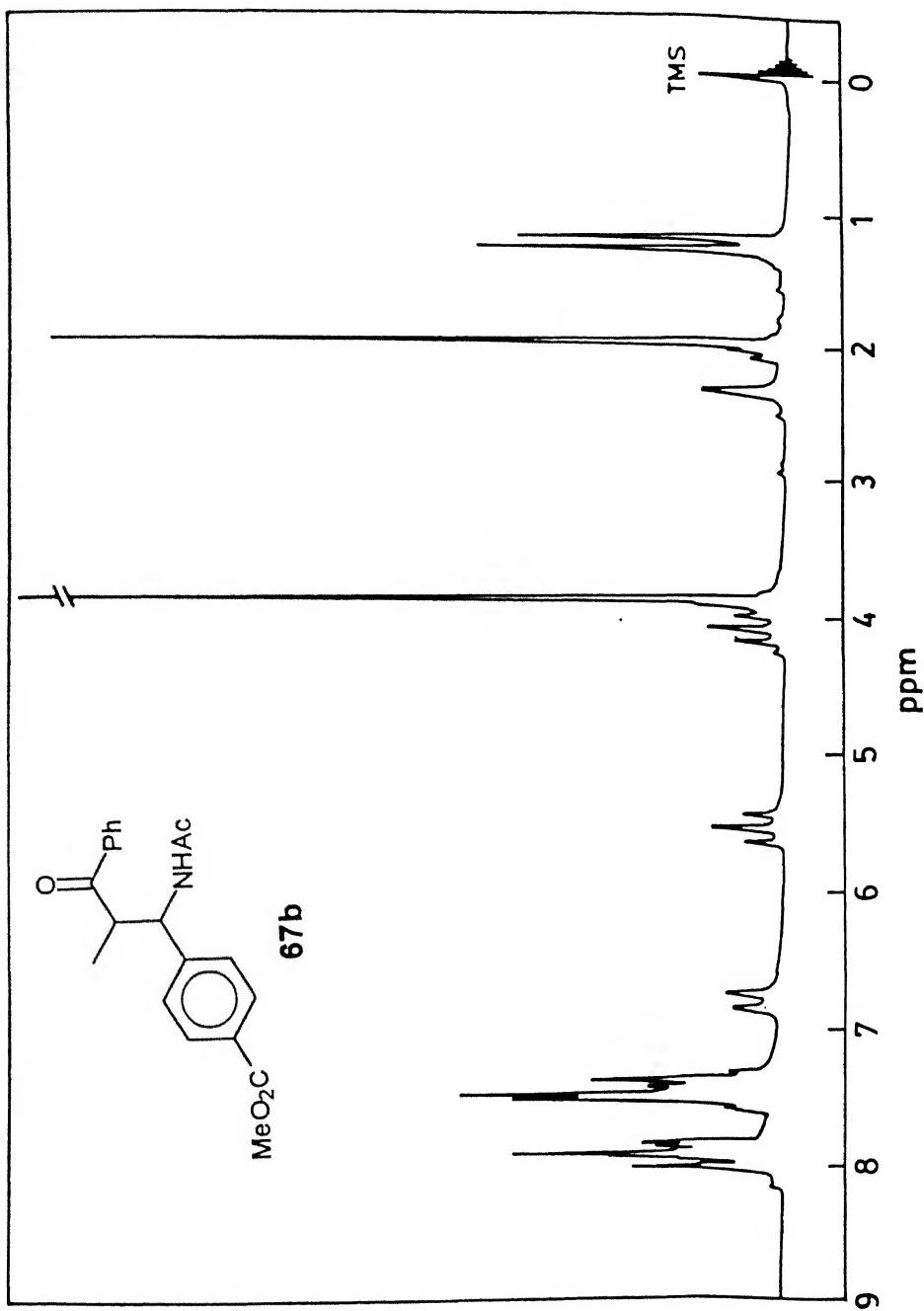


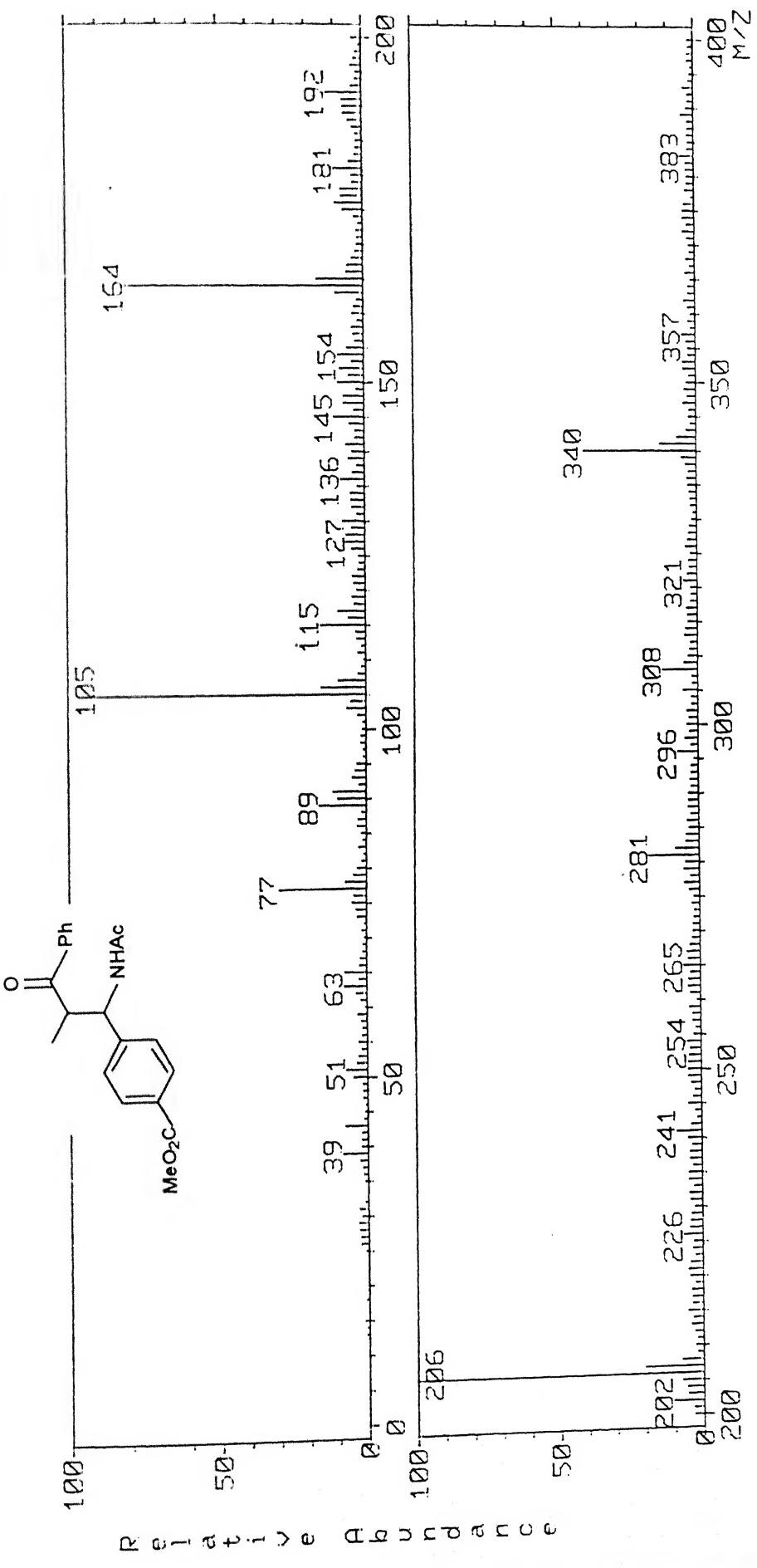


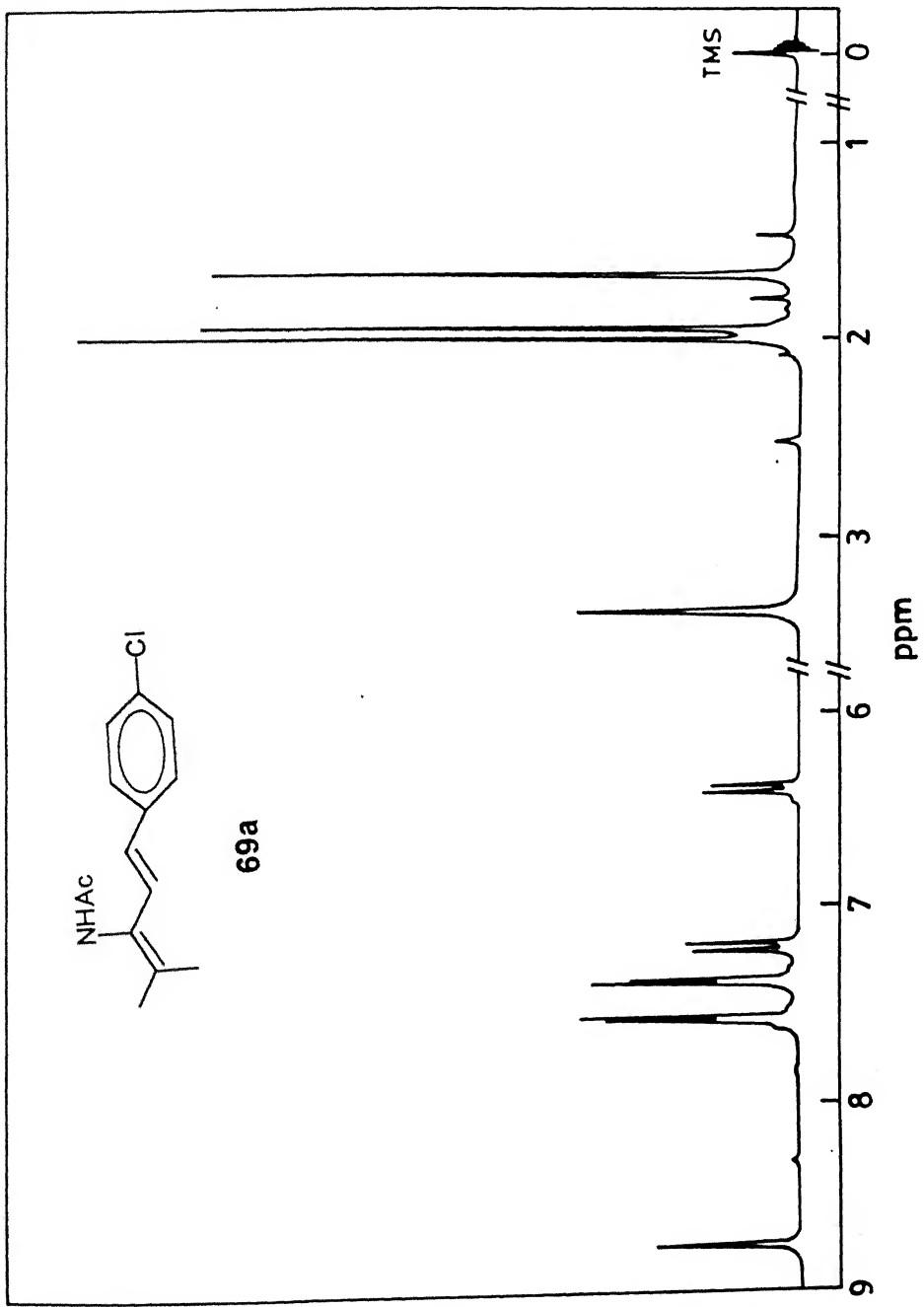


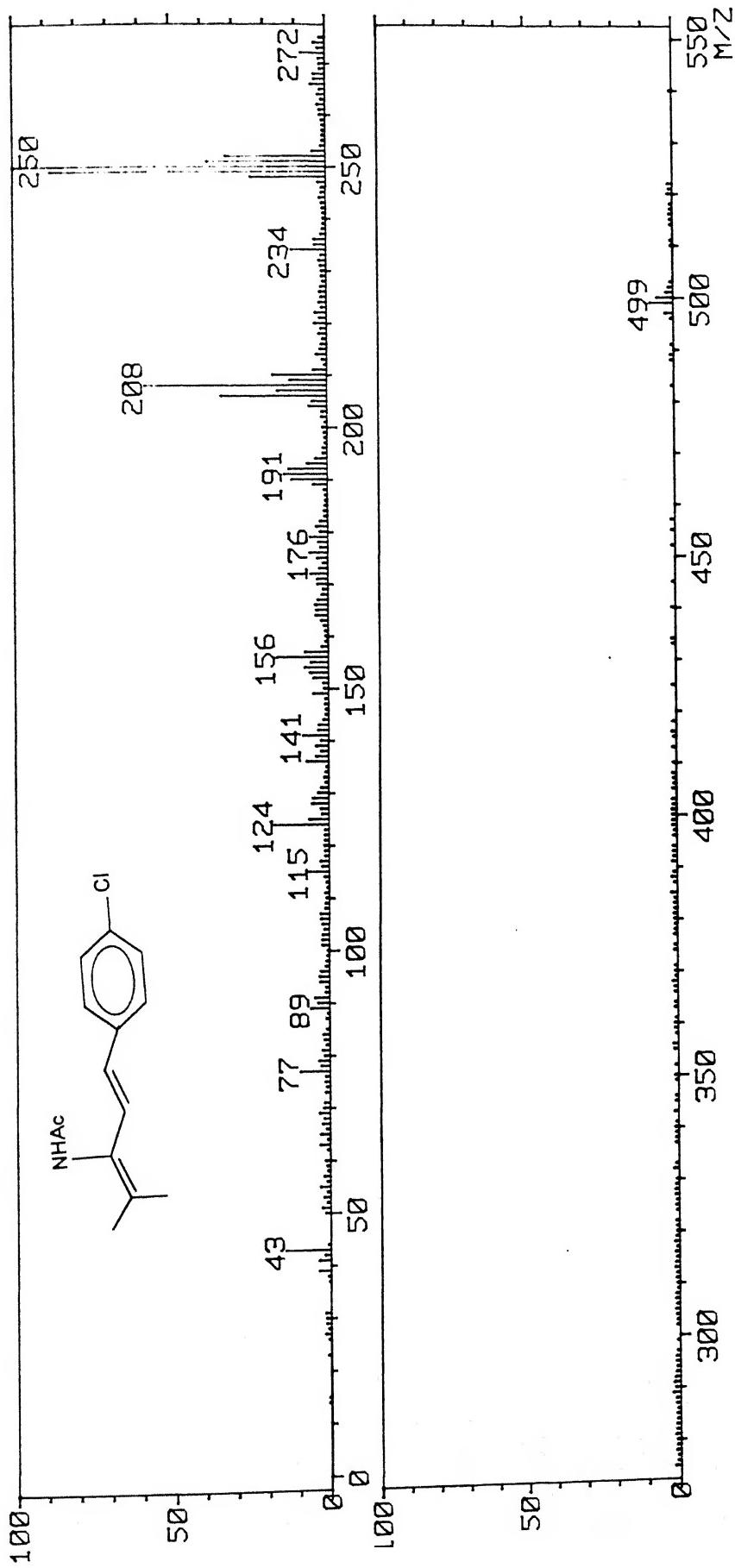












## 2.4 REFERENCES

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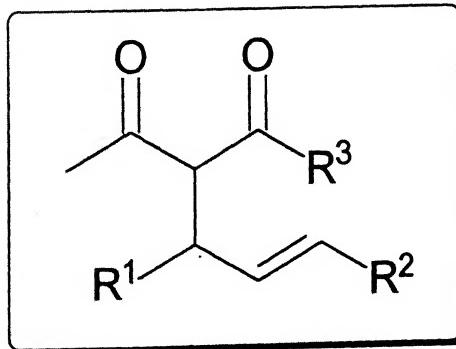
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# Chapter 3

## COBALT(II) CATALYZED ALLYLATION OF 1,3-DICARBONYL COMPOUNDS WITH ALLYL ACETATES.

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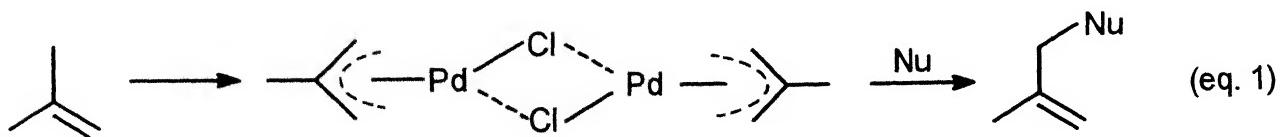


### 3.1 INTRODUCTION

Palladium catalyzed allylic alkylations has emerged as an outstanding transformation in the domain of synthetic organic chemistry. The versatility of this methodology is clearly evident from the wide spread use that it enjoys in the contemporary organic synthesis.

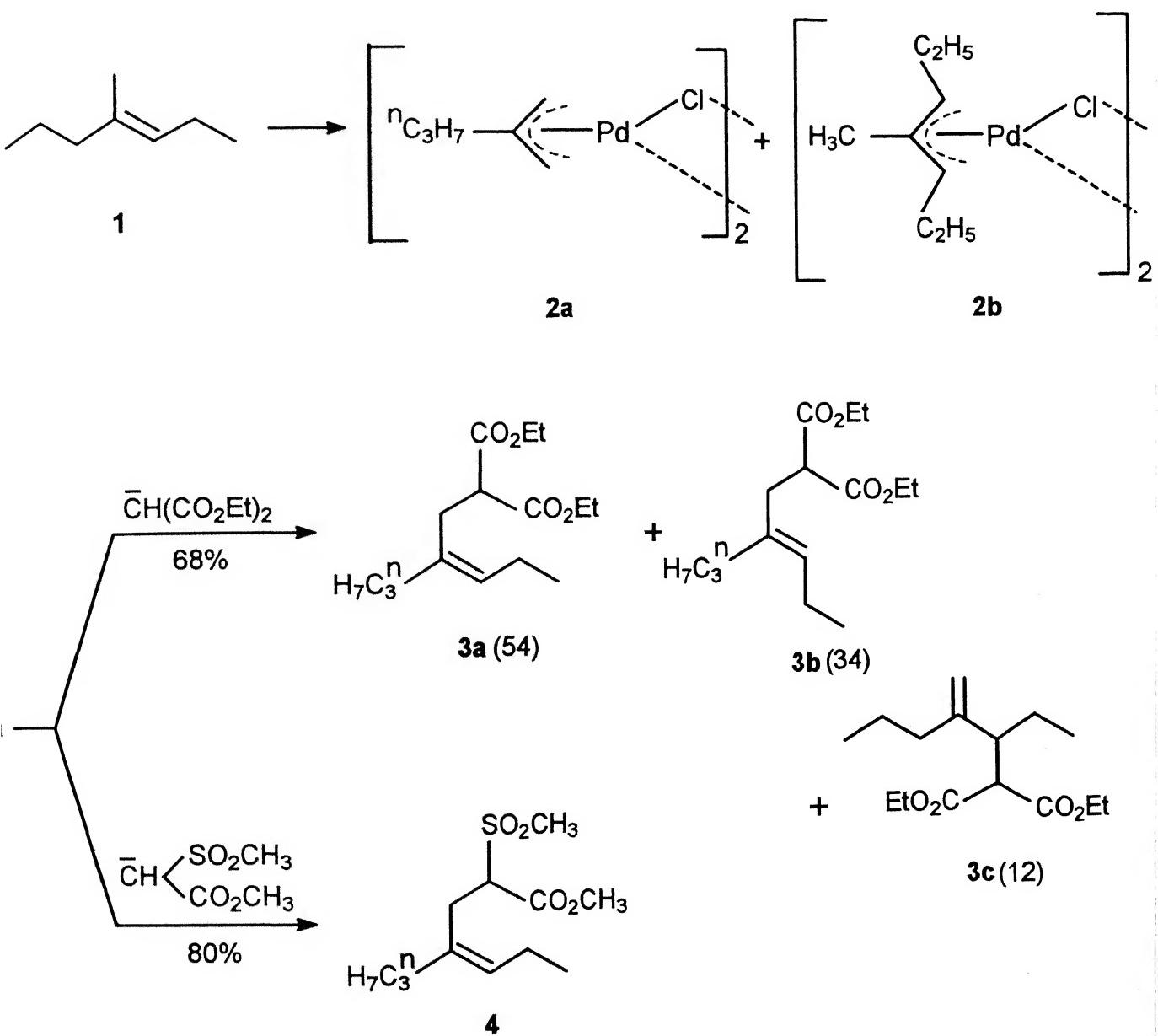
$\pi$ -Allyl complexes of palladium can be synthesized<sup>1</sup> by a number of methods from various allylic and olefinic compounds. These  $\pi$ -allyl complexes are stable, soluble in organic solvents, and can be handled easily. Also, they are formed *in situ* and can be used without isolation. These  $\pi$ -allyl complexes react with various nucleophiles.

Carbon-carbon bond formation of olefins can be achieved by the condensation of  $\pi$ -allyl palladium complexes with a polarizable anion (eq. 1).  $\pi$ -Allyl palladium complexes generated

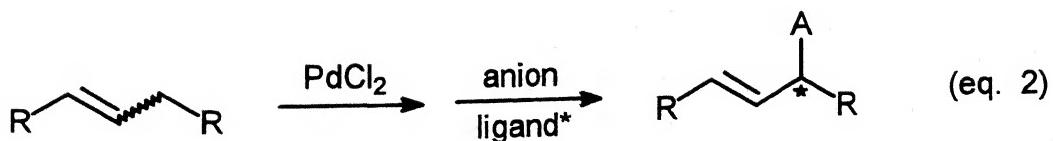


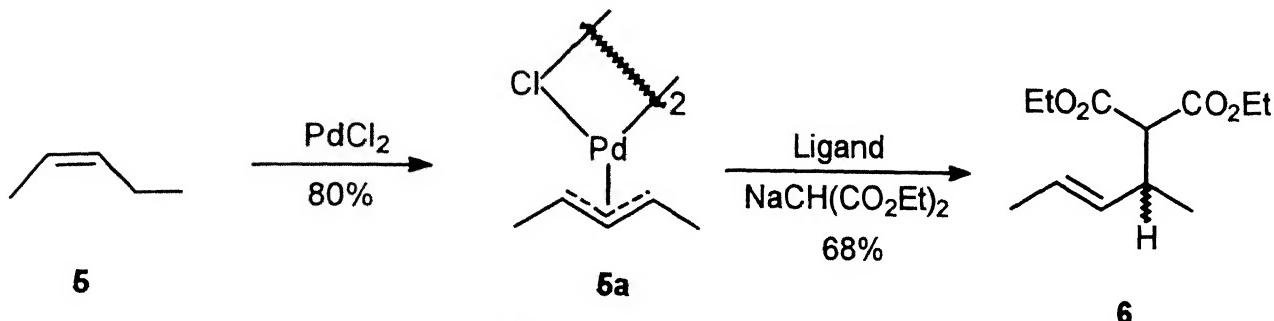
from the olefins, for example, 2-n-propyl-1-pentene **1** reacts with anion of malonate or methyl methysulfonyl acetate<sup>2</sup> in the presence of four equivalents of triphenylphosphine to give the products **3a-c** and **4** respectively (Scheme 3.1).

Optically active compounds can also be prepared<sup>3</sup> by the use of  $\pi$ -allyl palladium complexes. The use of chiral phosphines as the activating ligands has led to C-C bond formation of upto 74% optical yields (eq. 2). For instance, the alkylation of syn, syn-1,3-dimethyl- $\pi$ -allyl palladium chloride dimer **5a** (prepared by treatment of cis-2-pentene **5** with palladium chloride, NaCl, CuCl<sub>2</sub> and NaOAc in acetic acid) with diethylsodiummalonate yielded **6** in 26-66% optical purity with different optically active ligands such as (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenyl phosphino) butane [(+)-DIOP]<sup>4</sup>, (+)-O-anisylcyclohexylmethylphosphine [(+)-ACMP]<sup>5</sup> (Scheme 3.2).



Scheme 3.1



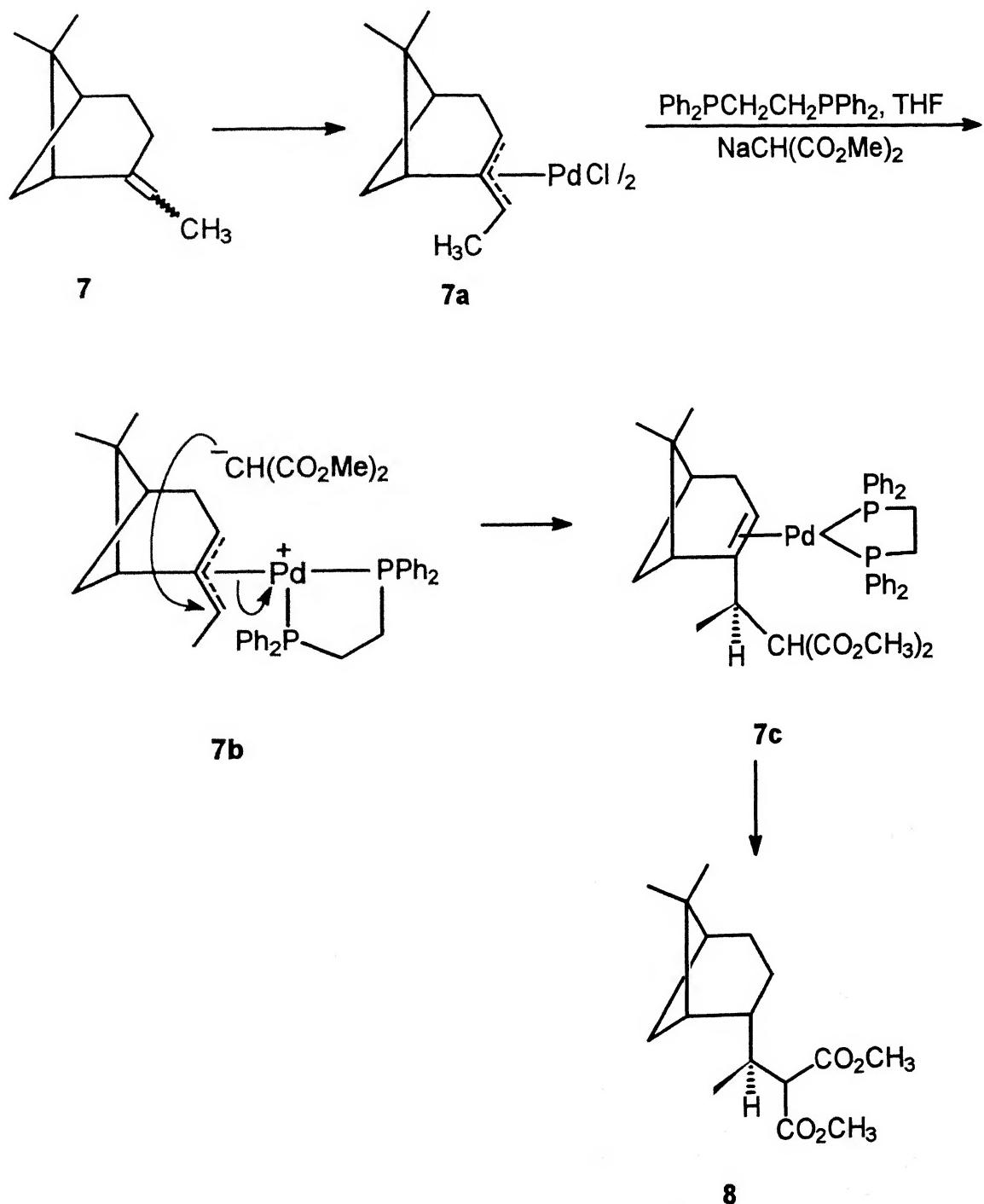


Trost and coworkers<sup>6</sup> have shown that the alkylation occurs on the face of the  $\pi$ -allyl unit opposite to that of the palladium. In conventional terms, the alkylation occurs by a normal inversion of configuration at carbon with palladium (0) becoming the leaving group (Scheme 3.3).

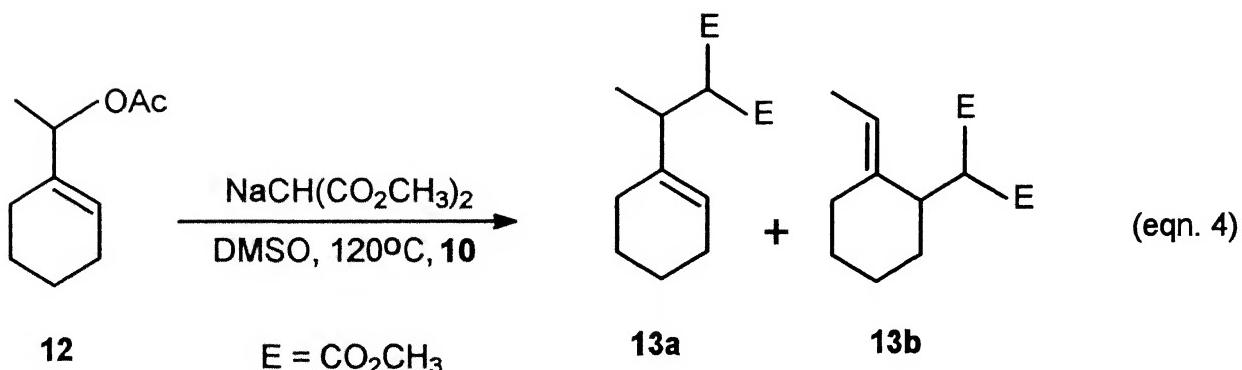
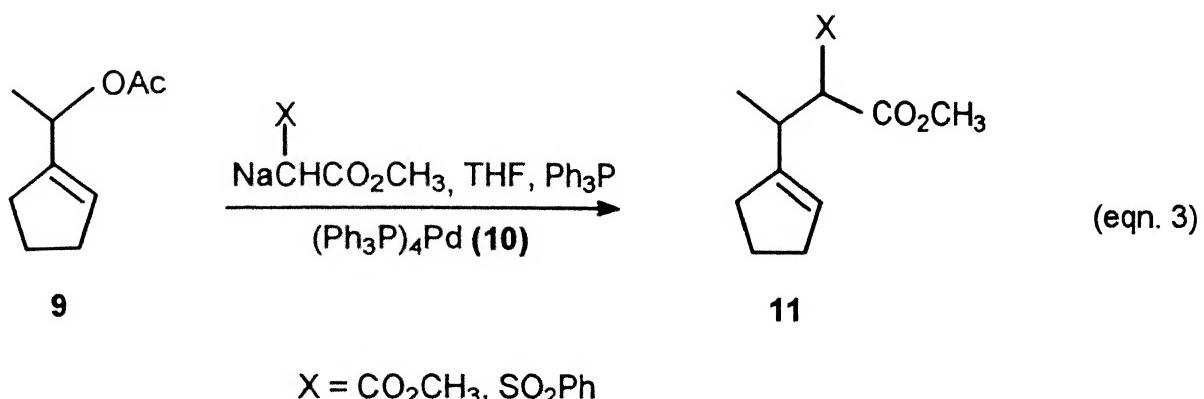
Interestingly, allylic alkylation can also occur with active methylene groups in the presence of catalytic amount<sup>7</sup> of various  $\pi$ -allyl palladium species generated from allyl acetates. Treatment<sup>8</sup> of allylacetates possessing an endocyclic olefin with the sodium enolate of either dimethyl malonate or methyl benzylsulfonyl acetate in refluxing tetrahydrofuran in the presence of tetrakis-(triphenyl phosphine) palladium (0) **10** and excess  $\text{PPh}_3$  led to exclusive alkylation at the exocyclic carbon atom, giving the product **11** in good yields (eq. 3).

In contrast to this, 1-(1-acetoxy ethyl) cyclohexene **12** was inert towards alkylation under the standard conditions of refluxing THF. Drastic conditions such as heating at  $120^\circ \text{C}$  in dimethyl sulfoxide is needed to produce an 85:15 mixture of **13a** and **13b** in 50% yield<sup>6,9</sup> (eq. 4).

Regioselectivity of palladium catalyzed allylic alkylations can be illustrated by the alkylation of trisubstituted allyl acetates, geranyl acetate **14a** and neryl acetate **14b** which exhibits a striking sensitivity to the nature of the nucleophile. In the case of geranyl acetate **14a**, the more sterically encumbered sulfonyl acetate attacks exclusively at the primary carbon atom, whereas with dimethyl malonate the product was formed in poor yield. In contrast to this, neryl acetate **14b** gave the major product of alkylation with dimethyl malonate arose from



Scheme 3.3



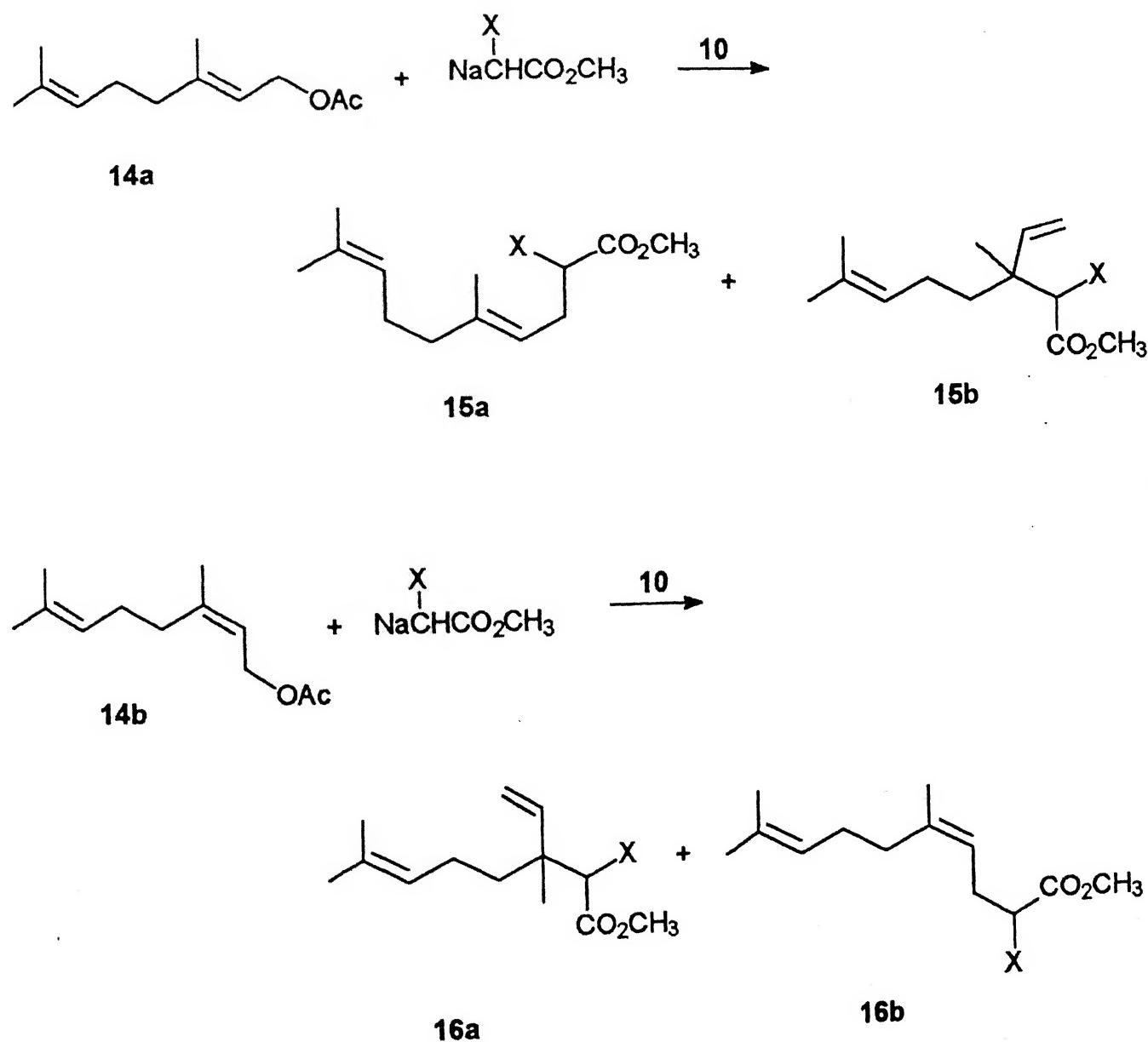
the attack at the tertiary carbon atom. With methylbenzylsulfonylacetate alkylation occurs at the primary carbon atom (Scheme 3.4).

Chemoselectivity of palladium catalyzed allylic alkylation can be illustrated by the reaction of bromoacetate **17** with nucleophile (Scheme 3.5).

Reaction of **17** with methyl benzenesulfonyl acetate in hot DMF produced **18a** as the exclusive product. In contrast, treatment of **17** in refluxing THF with the palladium catalyst afforded **18b** in 77% yield.

The mechanism of the catalytic alkylations can be depicted as an initial dissociation of tetrakis-(triphenylphosphine) palladium (0) **10** into bis- or tris-(triphenylphosphine) palladium (0)<sup>10,11</sup> **10a** followed by formation of an olefin-palladium  $\pi$ -complex<sup>12</sup> **20a-b** (Scheme 3.6).

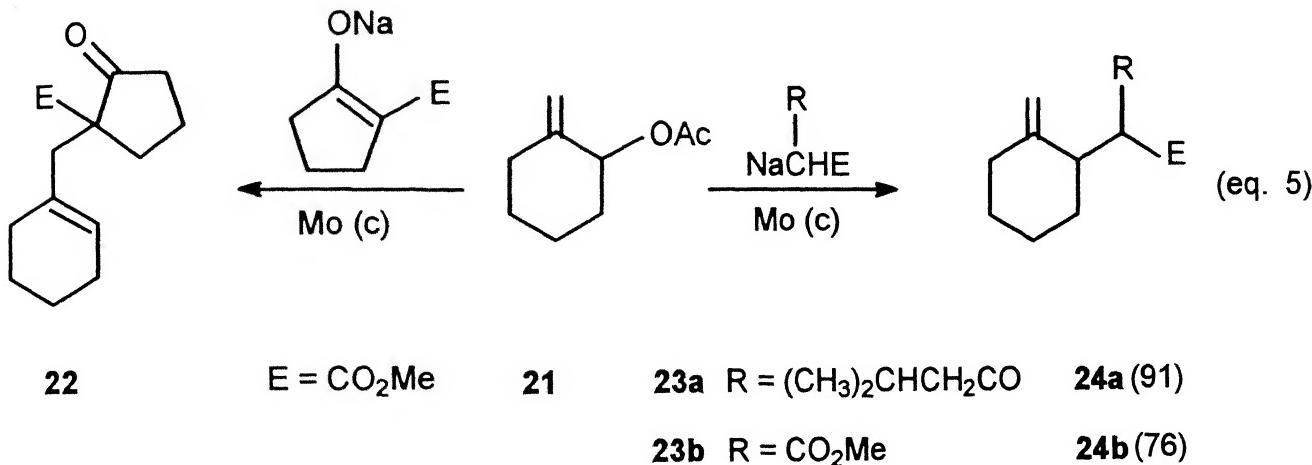
Alkylation with the stoichiometrically prepared  $\pi$ -allyl complexes proceed readily at room



Scheme 3.4

temperature<sup>13</sup>, while the catalytic process requires elevated temperatures (refluxing THF) with similar substrates, suggests that the oxidative addition<sup>14-17</sup> is the rate-determining step.

Depending on the nature of the nucleophile, molybdenum catalyzed allylic alkylations<sup>18,19</sup> are highly regioselective. This regioselectivity was first observed<sup>20</sup> with 2-acetoxy-1-methylene cyclohexane **21** as shown in eq. 5.

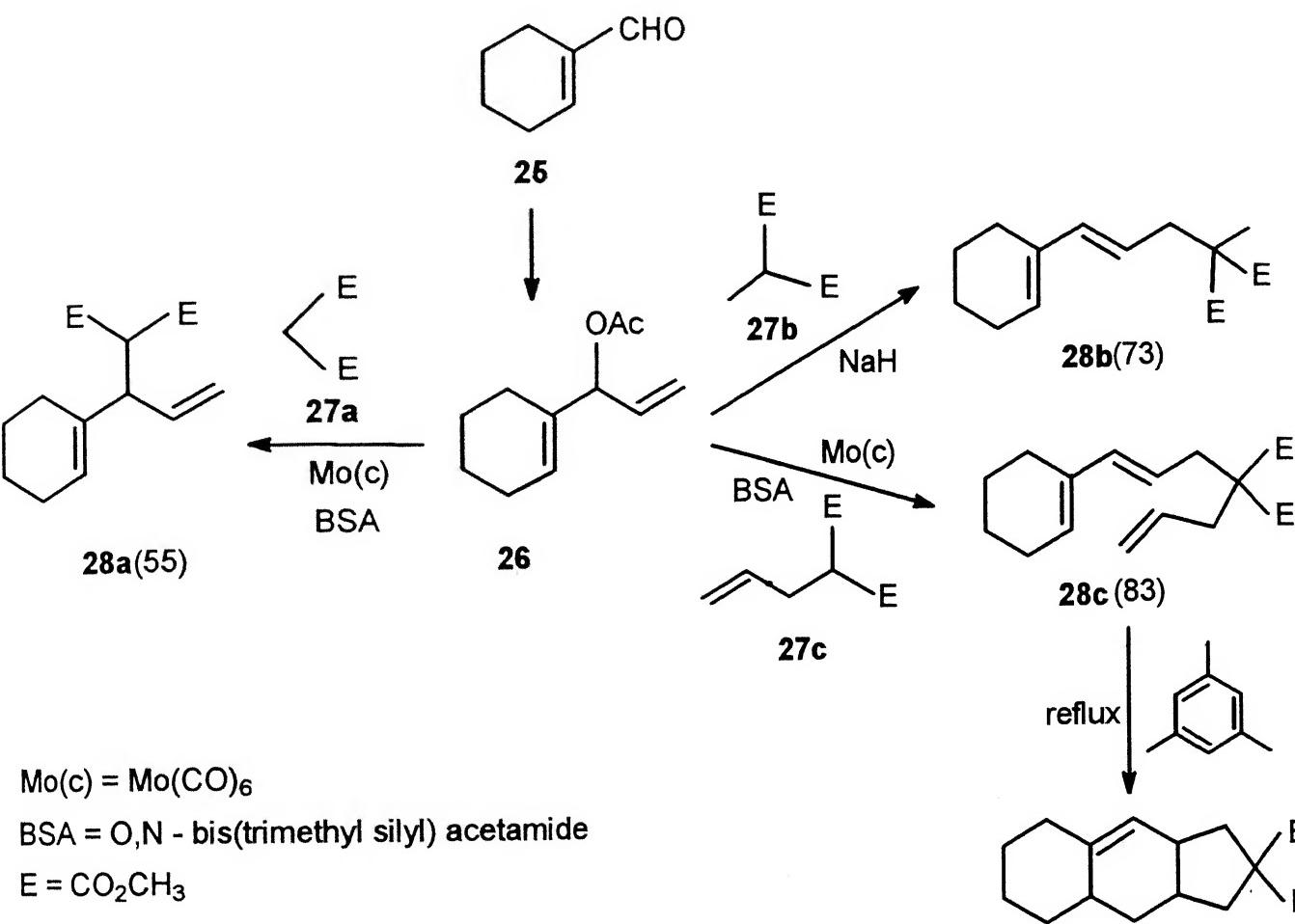
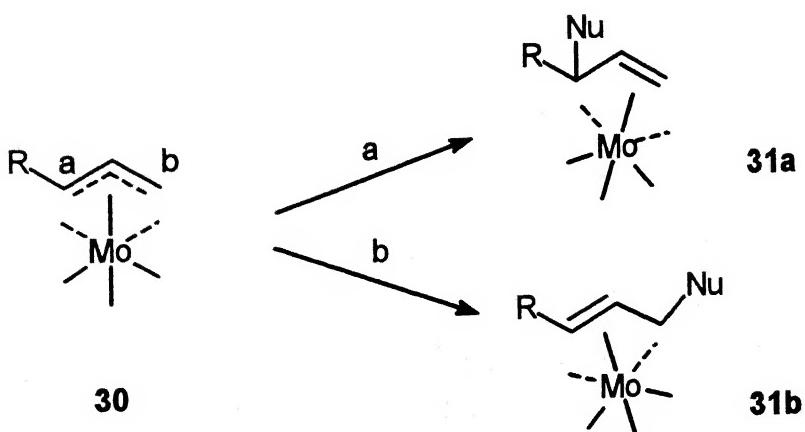


In the presence of NaH, 5% Mo(CO)<sub>6</sub> (Mo(c)) in PhCH<sub>3</sub> at 110° C, the sodium salt of 2-carbomethoxy cyclopentanone gave **22** while the sodium salt of an acyclic  $\beta$ -ketoester **23a** and of dimethyl malonate **23b** gave the products **24a** and **24b** respectively, of exclusive attack at the ring carbon rather than the side chain carbon.

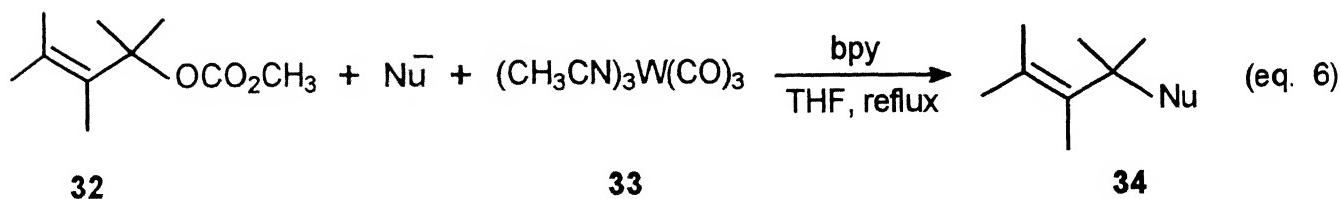
Molybdenum catalyzed allylic alkylations offer complementary regiochemical behaviour with malonate **27a** and substituted malonates **27b-c** as shown in the Scheme 3.7.

This unusual divergence in regioselectivity between dimethyl malonate and other nucleophiles appear from an intricate balance among reactivity of the anion, its steric demands, the charge distribution in the intermediate  $\pi$ -allyl system and the stability of the resultant olefin as well as the olefin-metal complex.

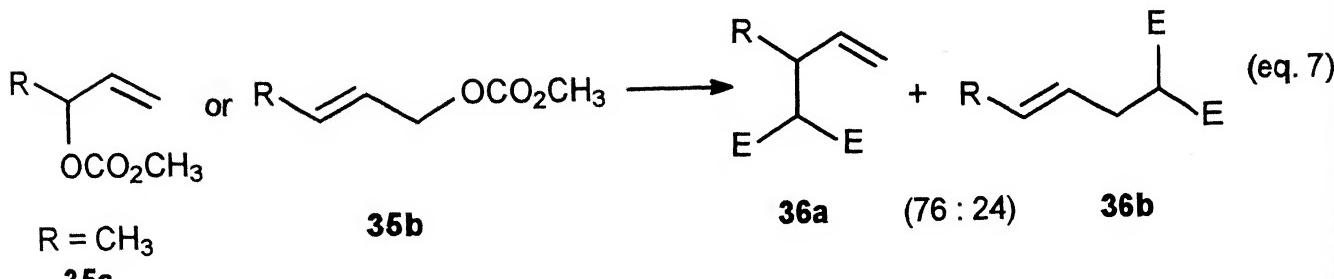
In an unsymmetrical complex such as **30** (Scheme 3.8), C(a) would be more electron deficient than C(b). The higher reactivity of the malonate anion and its minimum steric requirements leads to the sterically and electronically preferred olefin-Mo complex as the initial product. On the other hand, introduction of a single alkyl substituent makes the steric demands of the nucleophile sufficiently to attack at the C(b).

**Scheme 3.7****Scheme 3.8**

The unusual regio- and chemoselectivity of allylic alkylations<sup>19,21-23</sup> were observed with tungsten templates<sup>24-26</sup>. Allylic alkylation occurs with allyl carbonates **32** and the nucleophile such as dimethyl sodiomalonate in the presence of tungsten complex **33** (eq. 6). Use of a stronger  $\sigma$ - donor type ligand such as bipyridyl (bPy) facilitates opening of a coordination site on the tungsten led to the better yields.

**32****33****34**

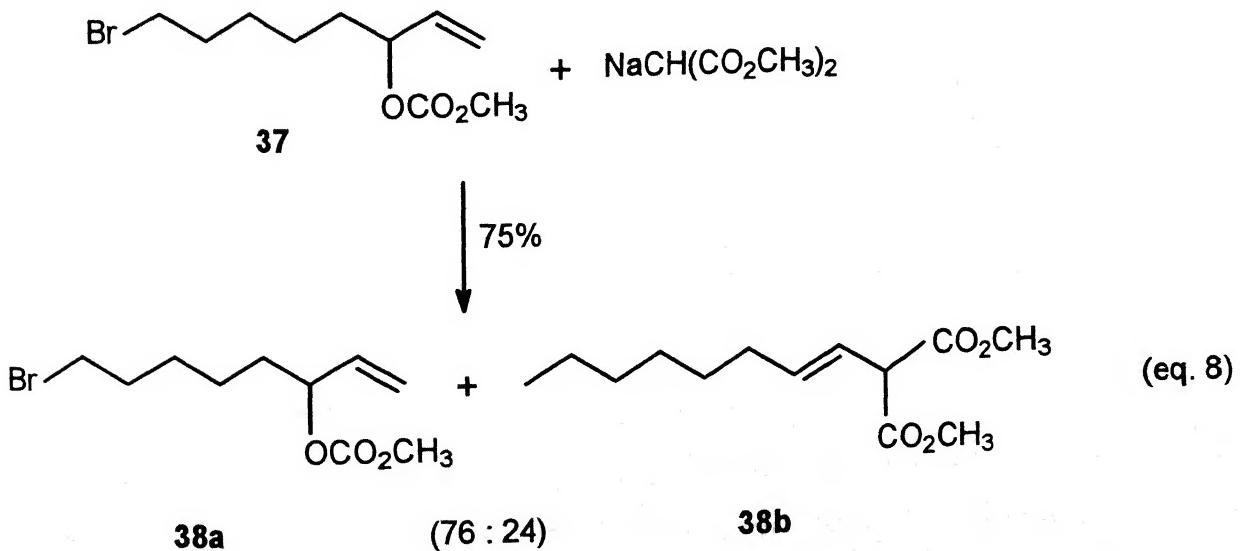
In the tungsten catalyzed reactions, alkylation occurs exclusively at the more substituted end regardless of the nucleophile (eq. 7).

**35a****35b****36a**

(76 : 24)

**36b****35b**

These tungsten catalyzed reactions are chemoselective. The bromocarbonate **37** exhibits only displacement of the allyl carbonate (eq. 8).

**38a**

(76 : 24)

**38b**

Transition metal complexes have emerged as an important tools for the synthesis of many natural products.<sup>9c,21a,27-29</sup> Among these,  $\pi$ -allyl palladium complexes have proven to be versatile in this area.

Manchand and coworkers<sup>31</sup> have synthesized Vitamin A<sup>32</sup> by using  $\pi$ -allyl palladium complex<sup>33</sup> **40a** which was generated from prenyl acetate **40**. Treatment of complex **40a** with the sulfone<sup>34,35</sup> **39a** which was prepared from vinyl- $\beta$ -ionol **39** and benzenesulfinic acid produced **41**. Elimination of benzenesulfinic acid from **41** afforded the Vitamin A **42** with all trans-geometry (Scheme 3.9).

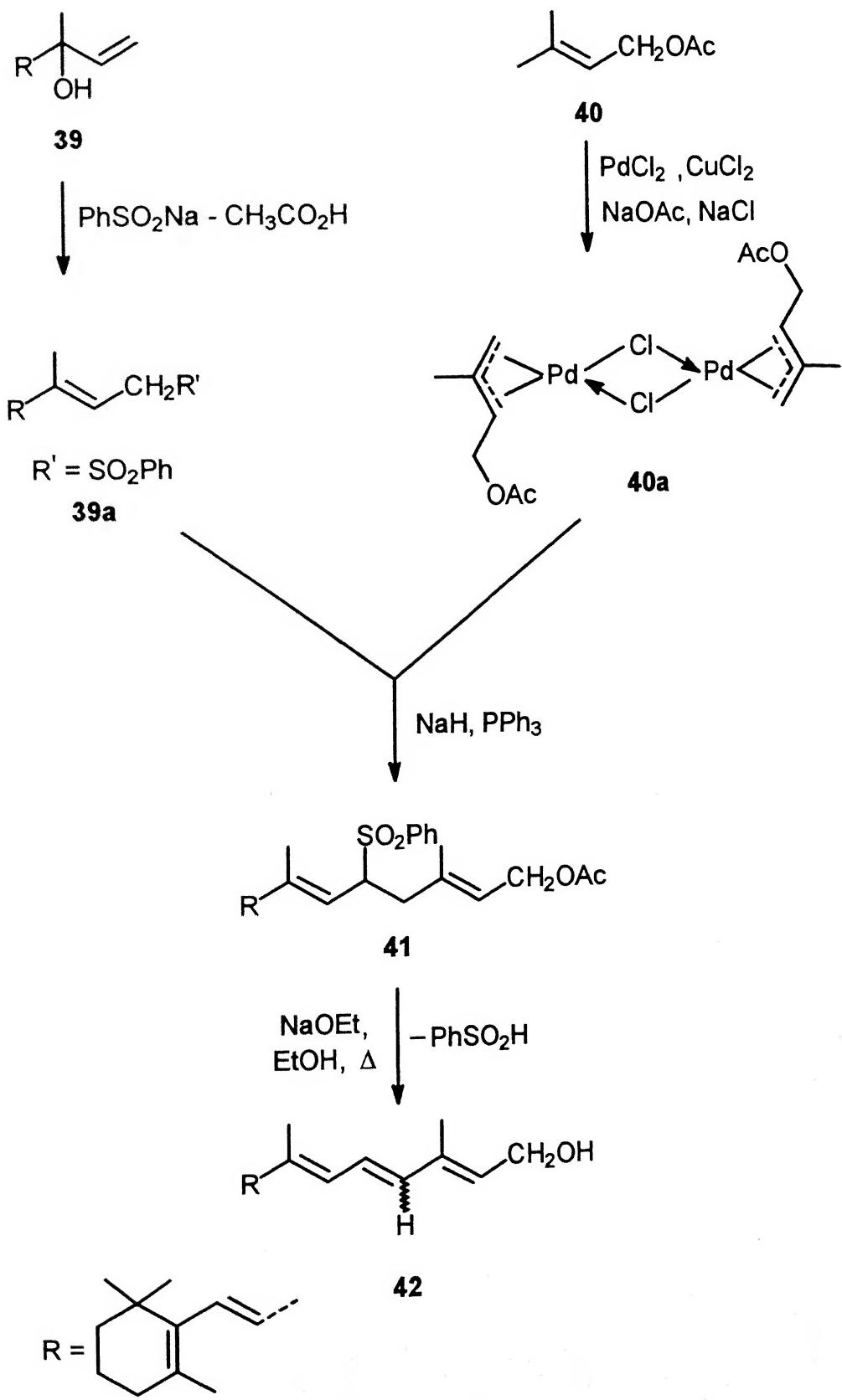
Palladium-assisted intramolecular alkylation facilitates the formation of large rings<sup>36,37</sup>. Trost and coworkers<sup>38</sup> have synthesized the naturally occurring macrolide ( $\pm$ )-recifiolide<sup>39,40</sup> **46** via the palladium-assisted cyclization reaction. The alcohol portion **44** was synthesized starting from tert-butyl dimethylsilyl ether **43**. Acid portion **45a** was prepared from the  $\beta$ ,  $\beta$ ,  $\beta$ -trichloroethyl ester of 5-bromopentanoic acid **45**. Alkylation of the sodium salt of methyl phenyl sulfonylacetate with **45** followed by reductive hydrolysis<sup>41</sup> afforded the acid **45a** (Scheme 3.10).

Allylic alkylations catalyzed by palladium (0) complexes have proven quite versatile for structural elaboration<sup>21a,42,43</sup>. This methodology has been extended successfully to the synthesis of many natural products.

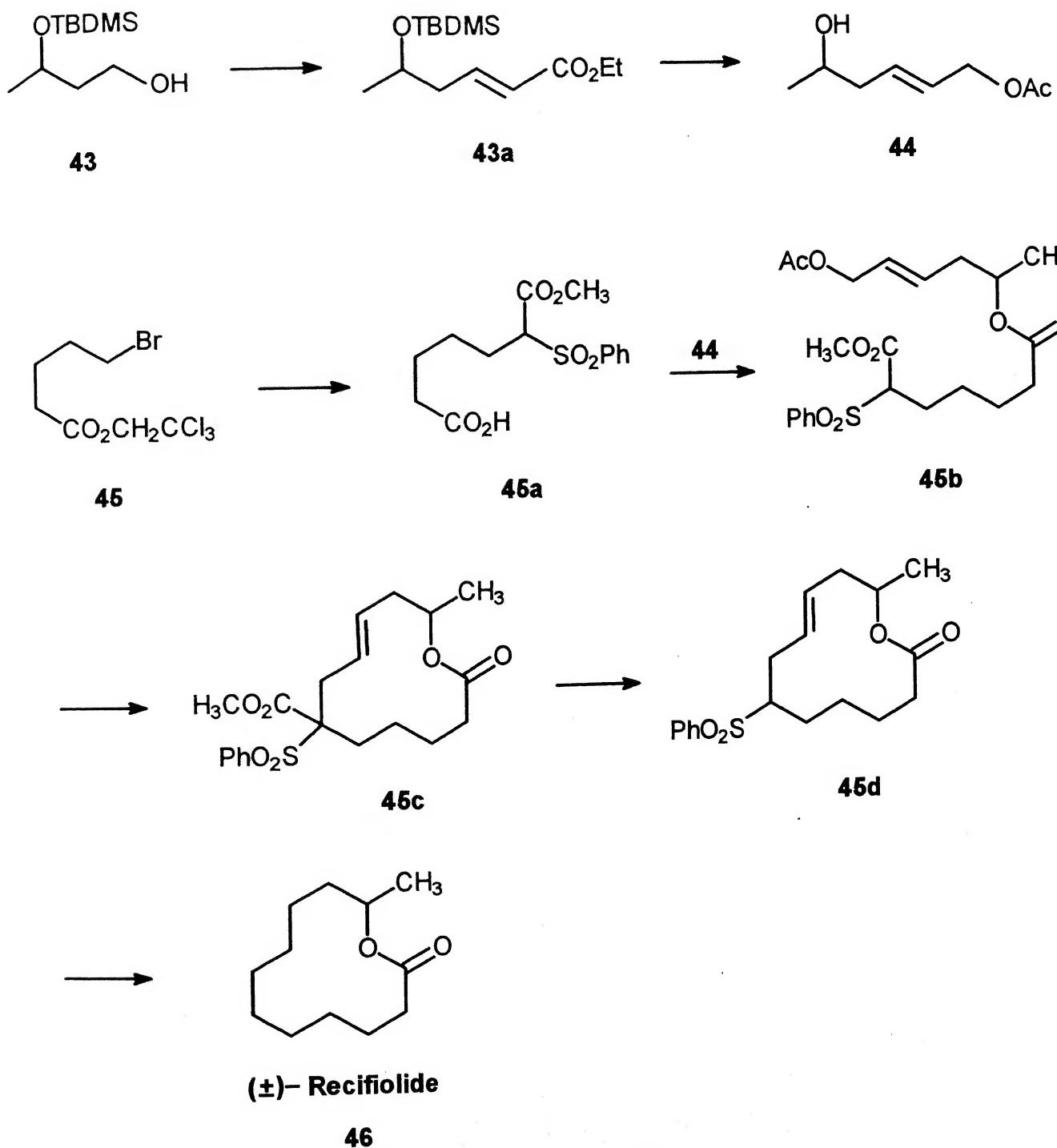
Pyrenophorin<sup>44</sup> **51**, an antifungal and cytostatic agent has been synthesized<sup>45</sup> from aldol **47** as outlined in Scheme 3.11. The key alkylation reaction proceeds regioselectively to give **48**. In order to merge with the Gerlach intermediate<sup>46</sup> **50b**, **48a** was transesterified to the methyl ester **48b** and finally the intermediate **50** was transformed into the required product **51**.

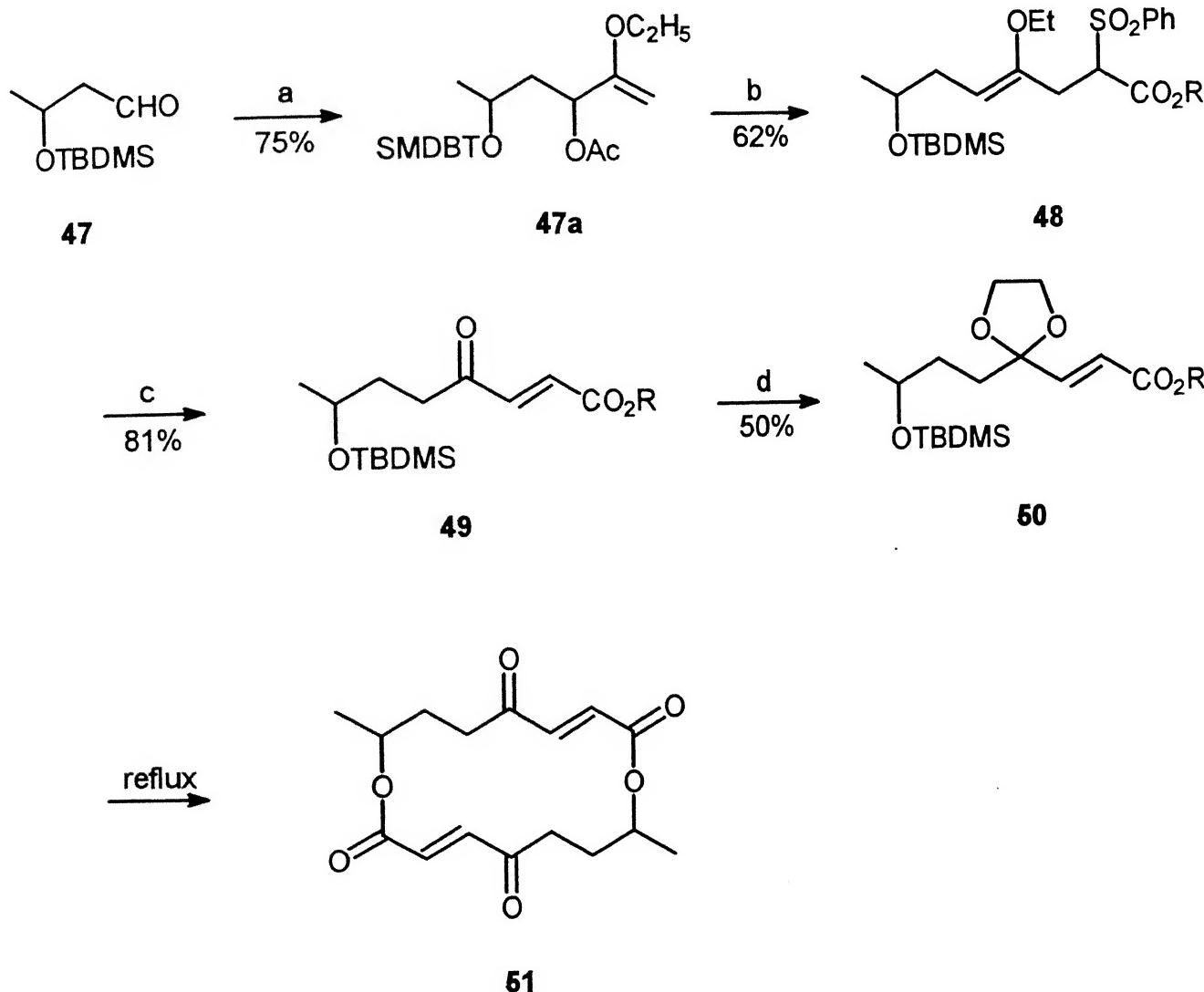
Allylic alkylation is a potential route for the synthesis of enedione<sup>47</sup> **57**, which is a potentially versatile intermediate for the synthesis of biologically active fused five-membered ring natural products<sup>48</sup>. The synthesis of **57** is outlined in the Scheme 3.12.

Palladium(0) catalyzed reaction of 2-methyl 1,3-cyclopentanedione **52** with 2-ethoxy-3-acetoxy-1-propene **53** afforded the crystalline enol ether **54a**. Treatment of **54a** with NBS and water<sup>49</sup> produced bromo ketone **55a** which was then directly converted to enedione **57**.



Scheme 3.9

Scheme 3.10

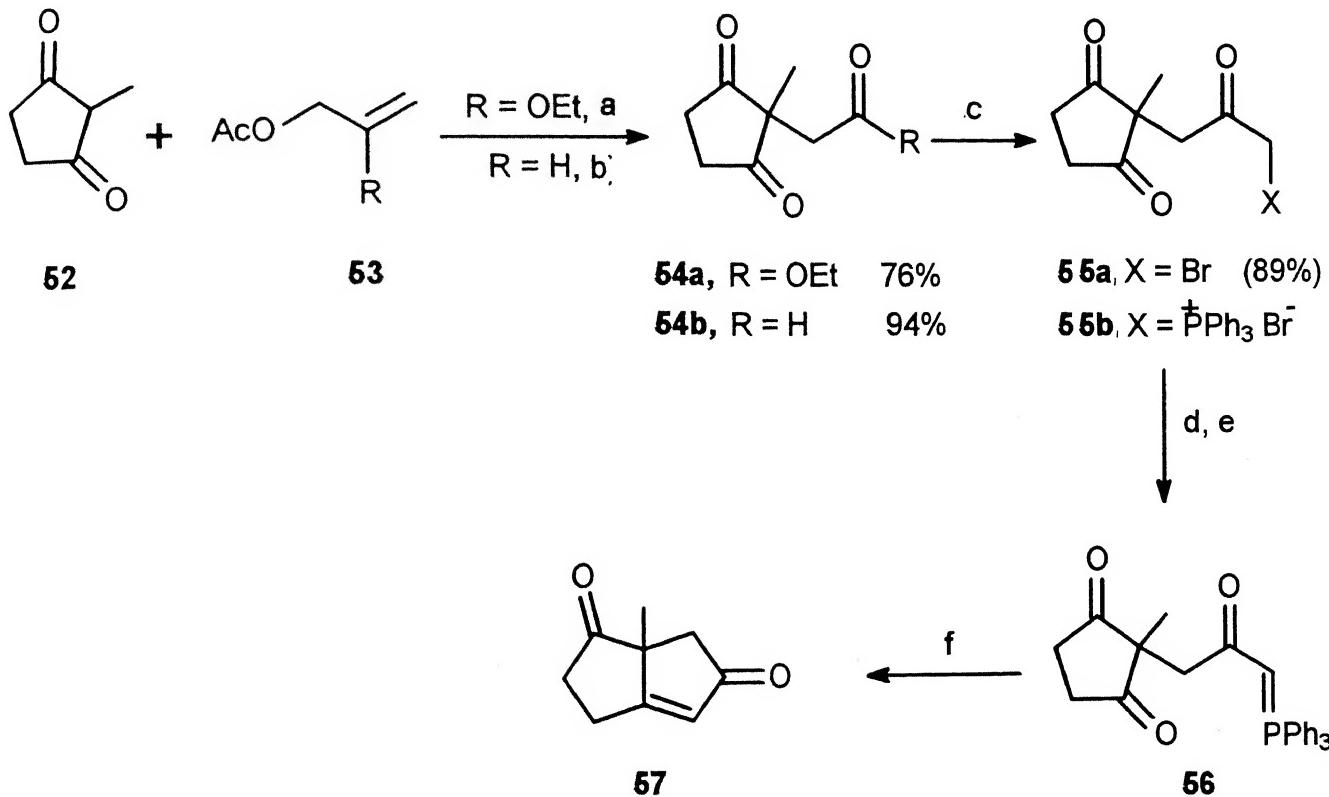


a, R = CH(CH<sub>3</sub>)<sub>2</sub>

b, R = CH<sub>3</sub>

- a) (i) CH<sub>2</sub>=C(Li)OC<sub>2</sub>H<sub>5</sub>, THF, -78° C (ii) Ac<sub>2</sub>O, C<sub>5</sub>H<sub>5</sub>N, r.t.
- b) (i) PhSO<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>C<sub>3</sub>H<sub>7</sub><sup>i</sup>, DBU, 13 mol% (Ph<sub>3</sub>P)<sub>4</sub>Pd, PhCH<sub>3</sub>, 80%  
(ii) NaOCH<sub>3</sub>, CH<sub>3</sub>OH, reflux.
- c) (i) Camphorsulfonic acid , (CH<sub>3</sub>)<sub>2</sub>CO, r.t. (ii) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, r.t.
- d) HOCH<sub>2</sub>CH<sub>2</sub>OH, Camphorsulfonic acid , PhH, reflux

**Scheme 3.11**

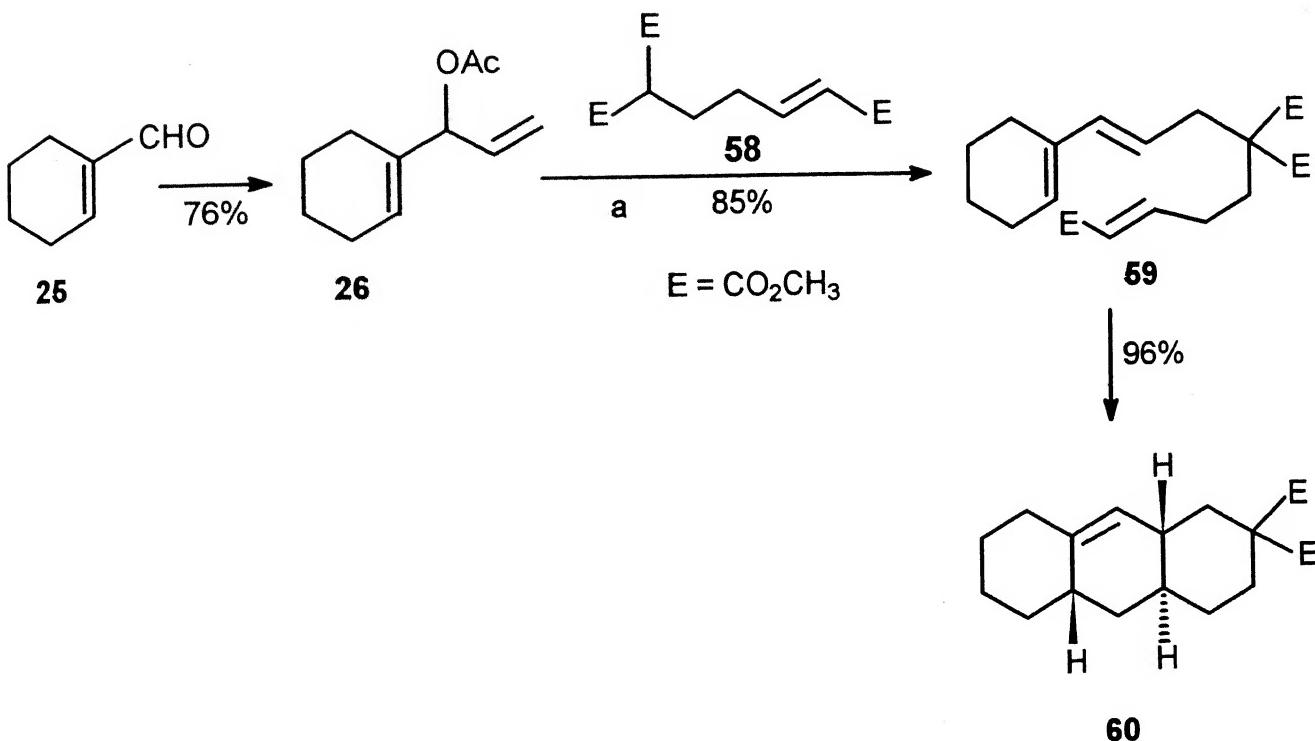


- a)  $\text{Pd(PPh}_3\text{)}_4$  1-10%, DBU, toluene,  $80^\circ\text{C}$  b)  $\text{Pd(PPh}_3\text{)}_4$  1%, THF,  $25^\circ\text{C}$ ,  
c) NBS (2 equiv.),  $\text{H}_2\text{O}$  (2 equiv.), DMSO,  $15\text{-}25^\circ\text{C}$ , d)  $\text{Ph}_3\text{P}$ , PhH,  $80^\circ\text{C}$ ,  
e) aq.  $\text{K}_2\text{CO}_3$ , f)  $40^\circ\text{C}$ .

**Scheme 3.12**

The intramolecular Diels-Alder reaction is an exceedingly powerful tool in the total synthesis of natural products<sup>50</sup>. The precursors for these reactions can be synthesized by transition metal catalyzed allylic alkylation<sup>51</sup>. For example, tricyclic systems **60** can be synthesized from cyclohexene-1-carboxaldehyde **25** in a three step operation (Scheme 3.13).

Polyene systems can also be generated by these metal-catalyzed reactions. As a result of the complementarity in the regioselectivity of the alkylation by palladium and tungsten catalyzed reactions, different substitution patterns result in the tetrahydroindanes. For instance, in palladium catalyzed reaction [2 mol %  $\text{Pd(OAc)}_2$ , 12.5 mol % dppb, 1-hexene, 5 mol % n-BuLi, THF, reflux], the  $\pi$ -allyl metal intermediate **62** suffers exclusive terminal

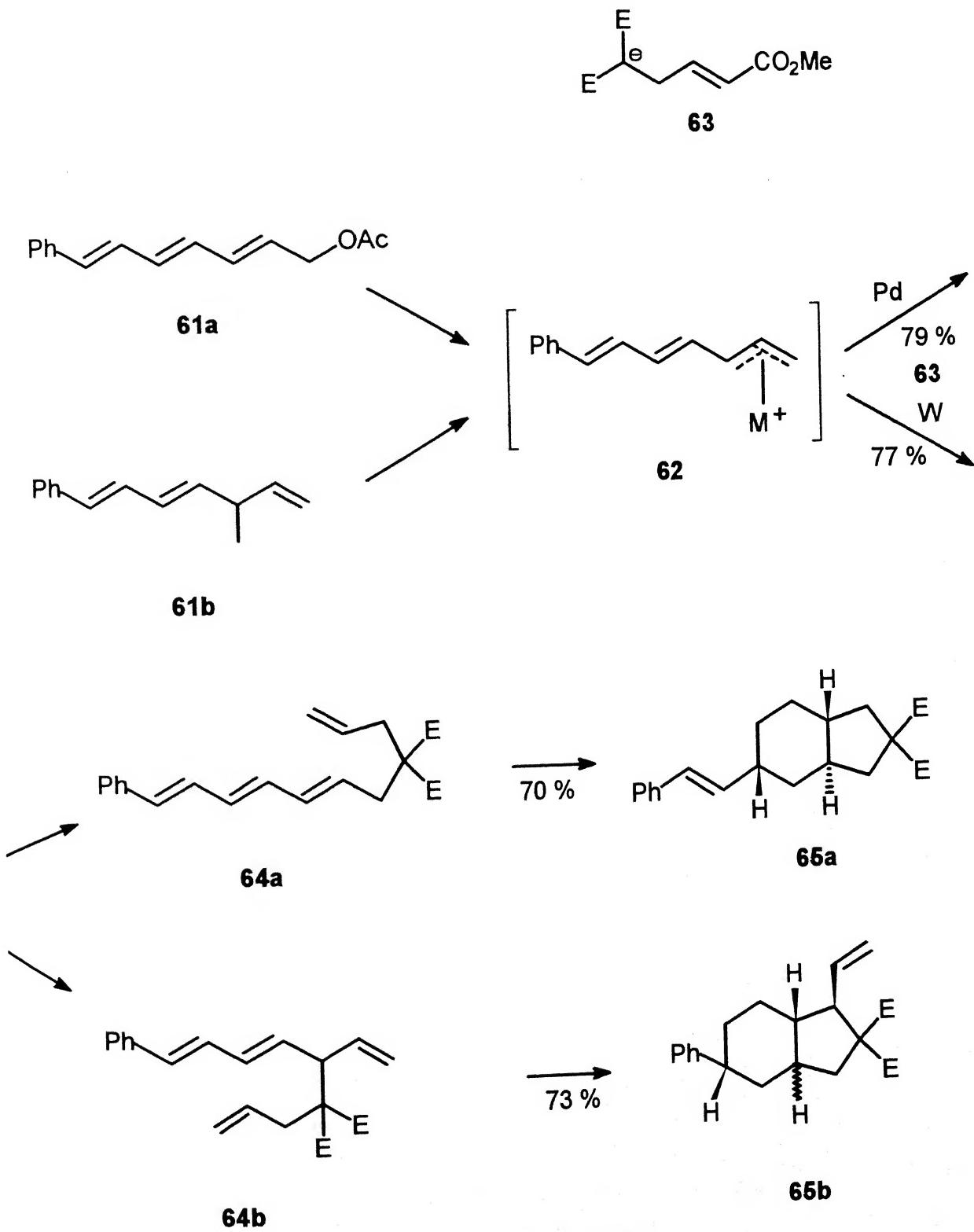


a) O, N - bis (trimethylsilyl) acetamide (BSA)

5 mol%  $(\text{PPh}_3)_4$ , THF, reflux.

Scheme 3.13

attack to give **64a**, whereas, in tungsten catalyzed reaction [30 mol %  $(\text{CH}_3\text{CN})_3\text{W}(\text{CO})_3$ , 30 mol % bpy, THF, reflux] internal attack occurs exclusively to give **64b** (Scheme 3.14).



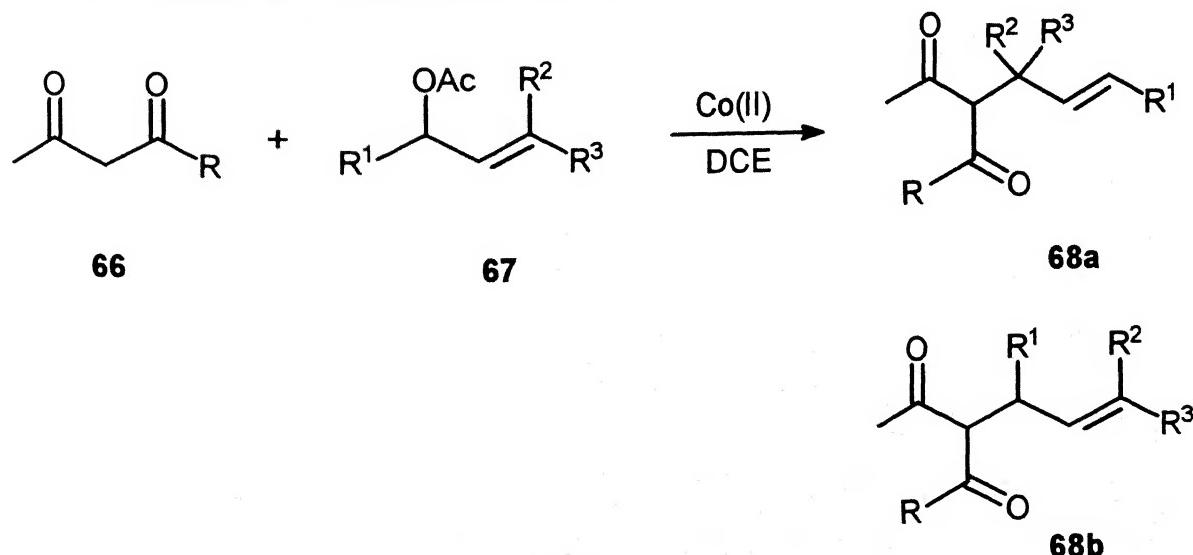
Scheme 3.14

These polyenes **64a** and **64b** serve as the best precursors for the intramolecular Diels-Alder reactions to provide substituted tetrahydroindanes **65a** and **65b** respectively.

## 3.2 PRESENT STUDY

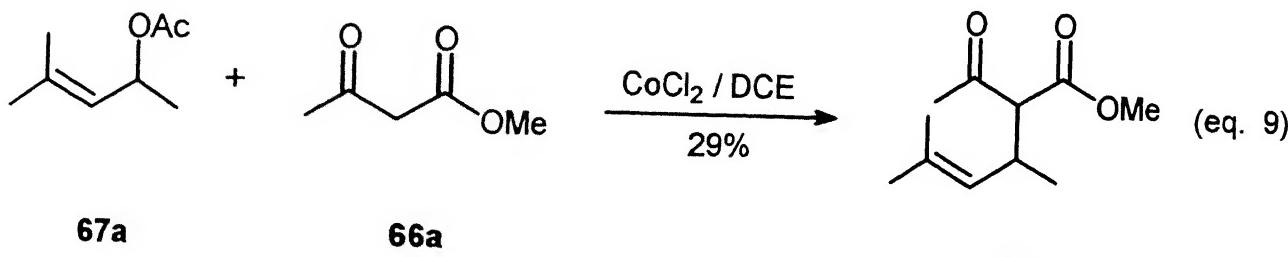
The formation of carbon-carbon bond involving high degree of regio- and stereo control has been a challenging task for synthetic organic chemist over the last few decades. As described in the previous section the palladium and molybdenum catalyzed allylation of 1,3-dicarbonyl compounds with allylacetates has emerged as an outstanding transformation in the domain of synthetic organic chemistry. These allylations are conducted on palladium and molybdenum complexes under basic conditions using stabilised anions derived from 1,3-dicarbonyl compounds. These reaction conditions are not compatible with base sensitive organic substrates and therefore bond formation on these molecules using palladium or molybdenum  $\pi$ -allyl protocol suffers from great disadvantage. In view of the above limitations we have undertaken study on cobalt(II) chloride catalyzed allylation of 1,3-dicarbonyl compounds with allylacetates. The following section deals with our results on this transformation.

Thus the treatment of allylacetate **67** with 1,3-dicarbonyl compounds **66** in the presence of cobalt(II) chloride (5 mol%) in 1,2-dichloroethane at  $70^0$  C for 8-12 h. afforded the allylated products **68a-b** in good yields (Scheme 3.15).

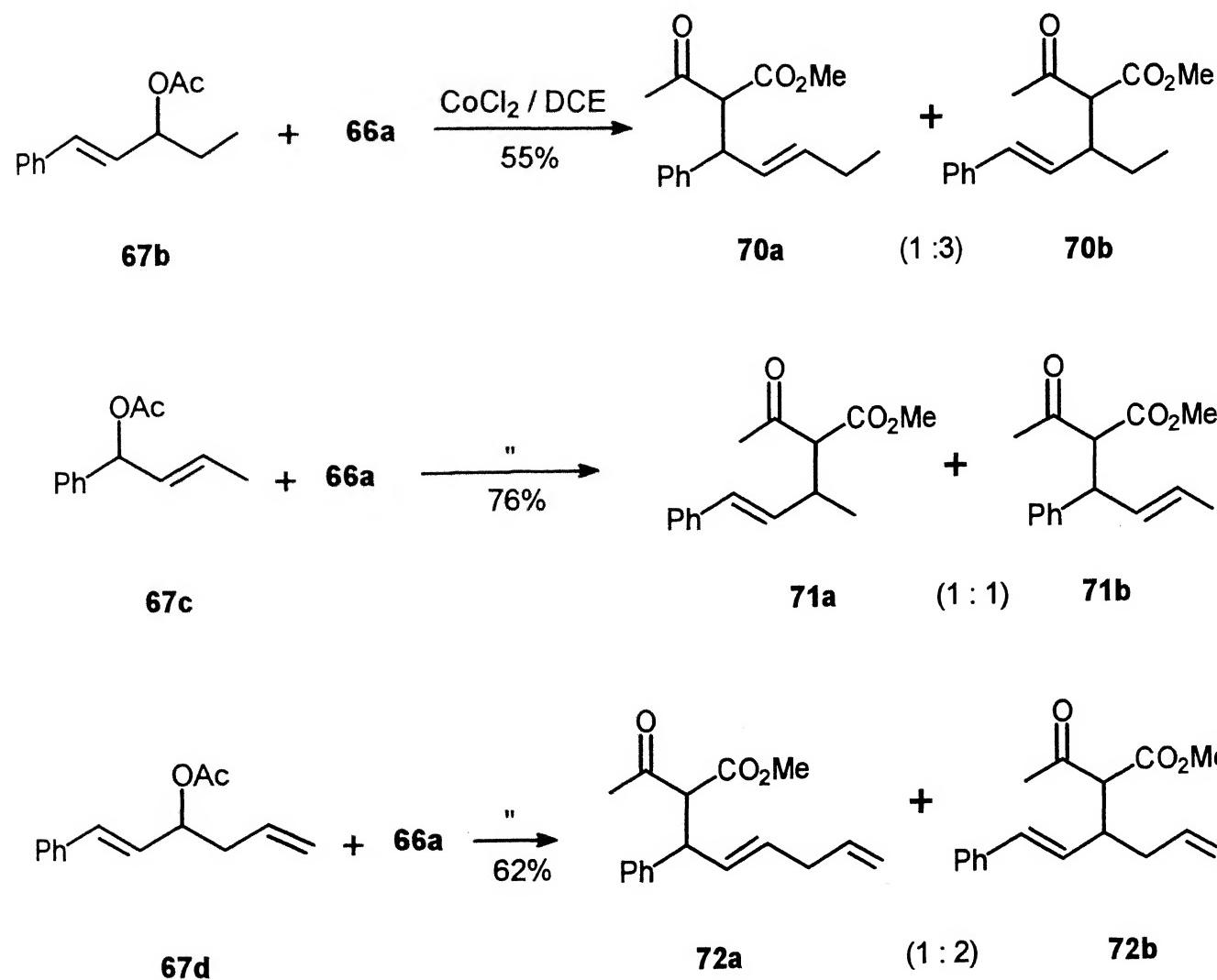
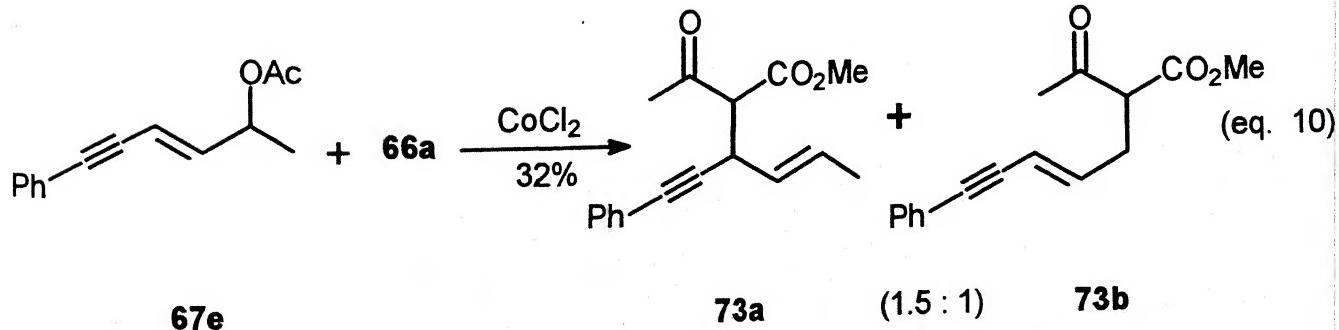


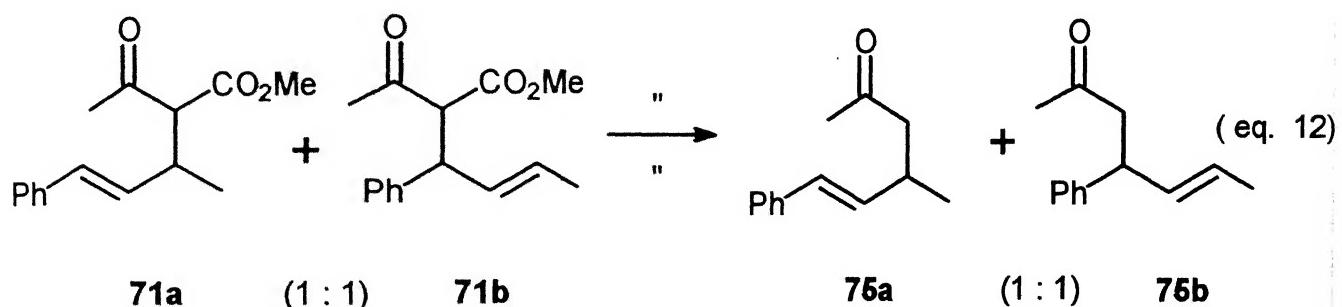
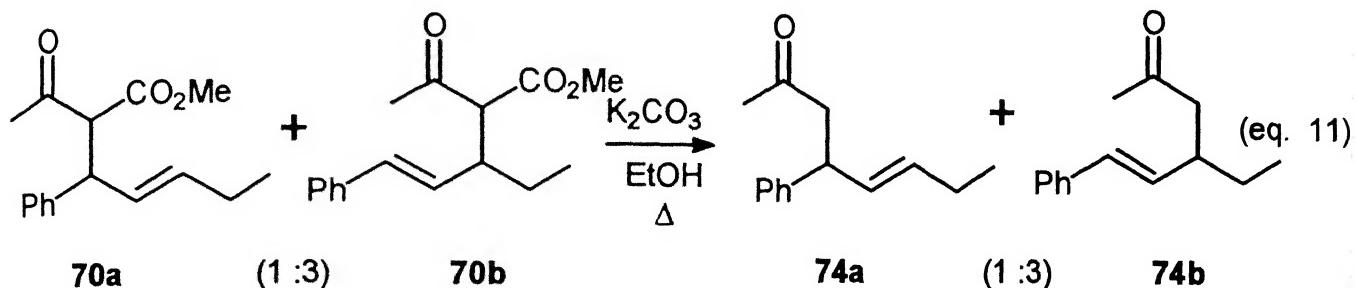
**Scheme 3.15**

The reaction of methyl acetoacetate **66a** with wide range of allylacetates afforded a mixture of regioisomers. However, the regio selectivity depend upon the structure of the allylacetate. It is clearly evident from the reaction in scheme 3.15 that this transformation is predominantly governed by steric factors as we get mainly one regioisomer. In the case of allylacetate **67a** which has tri-substituted double bond, the reaction affords only one regioisomer **69a** (eq. 9).

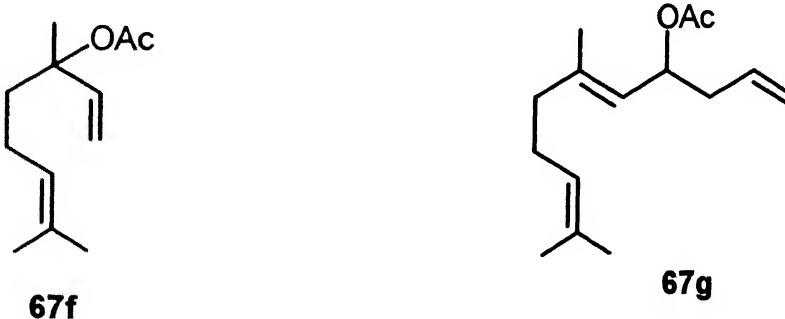


This observation clearly indicates the role of steric factors in these reactions. Interestingly, the reaction with allyl acetates **67b-d** derived from the derivatives of styrene provides the mixture of regioisomers **70a-b**, **71a-b**, **72a-b** respectively in nearly equal amounts (Scheme 3.16). These products consists of a nearly equal mixture of geometrical isomers. This clearly shows that conjugation of double bond with aromatic ring is not an important factor in this type of reactions. Similarly, enyneacetate **67e** also underwent this transformation to afford a mixture of regioisomers **73a-b** with predominantly E-geometry (eq. 10). Once again the extensive conjugation between aromatic ring, triple bond and double bond did not play any role towards the regiochemical outcome of this reaction. Thus the reaction with methyl acetoacetate and allylacetate appears to be controlled by the combination of stereo electronic effects. However, it is too premature to say anything with conviction as we have far too few examples on these substrates. It is also important to point out that the chemical yields are not high as a large part of allylacetate undergoes oligomerization. These reactions also suffer from poor diastereoselectivity as in most of the cases a mixture of diastereomers were obtained. The ratio of regioisomers further confirmed by decarboxylation of these diastereomers **70a-b**, **71a-b** to the corresponding ketones **74a-b**, **75a-b** respectively (eq. 11, 12) as a mixture of geometrical isomers. It is clearly evident from eq. 11 & 12 that the ratio of regioisomers remain same as the ratio prior to the decarboxylation.

**Scheme 3.16**

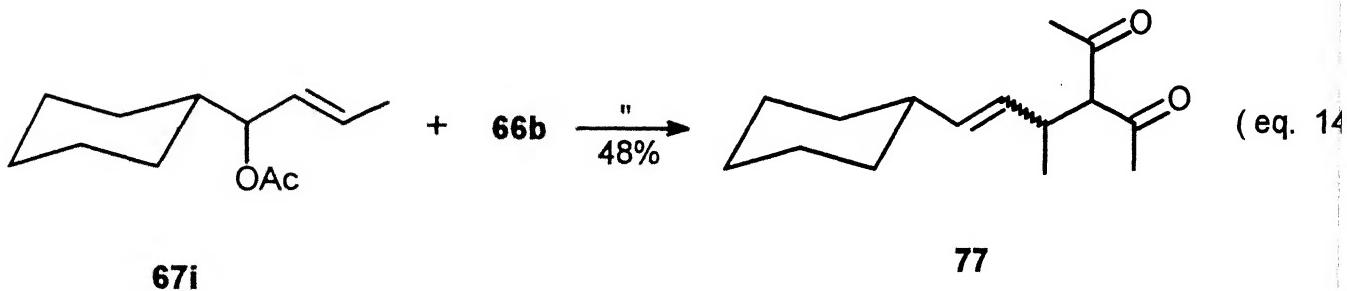
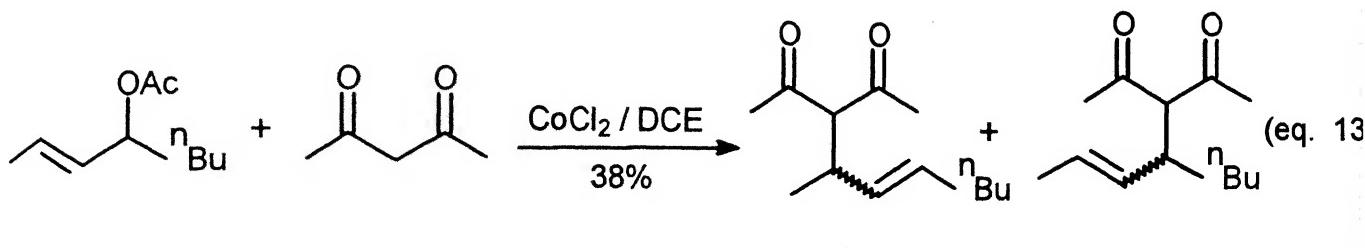


The reaction of methyl acetoacetate with linalylacetate **67f** does not give the expected allylated product, however, the latter appears to afford a cyclized product. Similarly, the reaction of methyl acetoacetate **66a** and triene acetate **67g** does not show any allylated product.

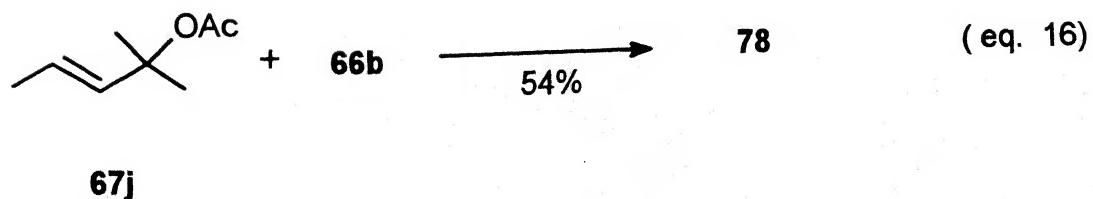
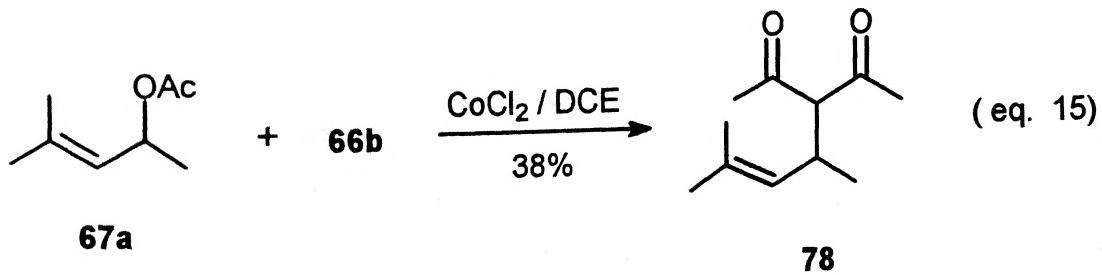


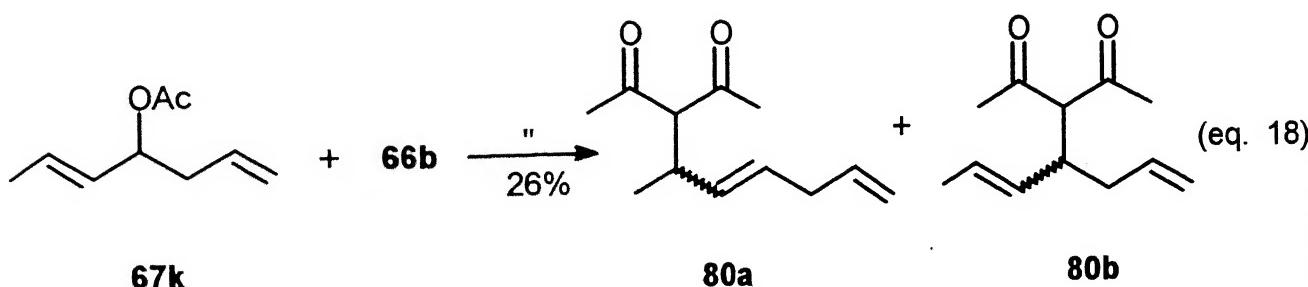
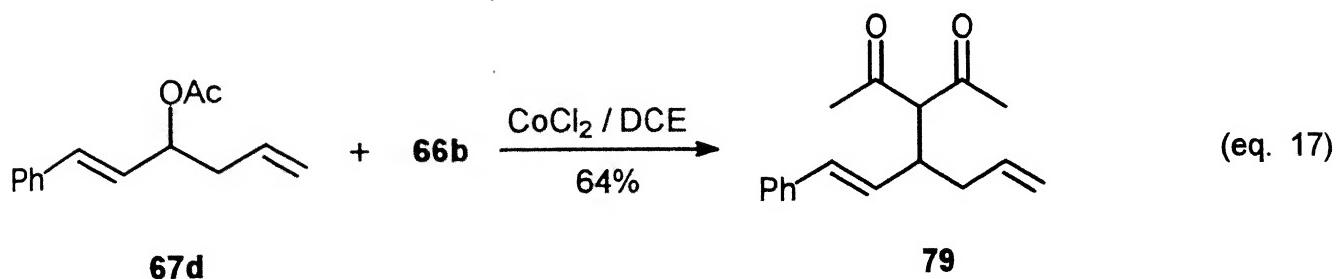
The reaction of allylacetate with acetylacetone **66b** is very facile as high yield of allylated products are obtained under these conditions. Thus a variety of allylacetates can be reacted with acetylacetone to give a mixture of regioisomers in which one of the isomer predominates, however, they were obtained as an equal mixture of geometrical isomers. Thus the linear acetate **67h** and the acetate containing cyclohexyl ring **67i** gave mainly one regioisomer **76b** and **77** respectively which is obtained by attack of acetylacetone on the carbon containing

methyl group (eq. 13, 14). Similarly, the reaction with secondary and tertiary acetates **67a** and **67j** gave mainly one regioisomer **78** which again indicates that this reaction is controlled

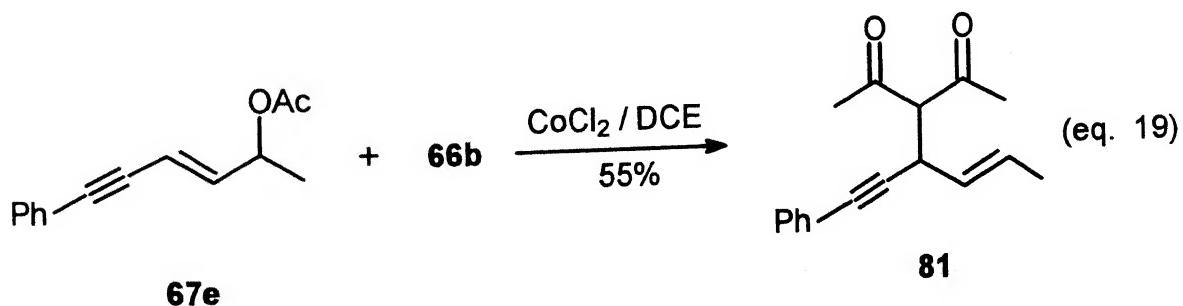


by steric factors (eq. 15, 16). The reaction with diene acetates **67d**, **67k** is also regioselective as one regioisomer **79** and **80a** respectively is obtained as the major product (eq. 17, 18). The latter was found to be a mixture of geometrical isomers. The selectivity in the case of acetate **67d** may be arising due to the ability of the double bond to come into conjugation with aromatic ring. The reaction with dienyl acetate **67e** is also highly regioselective and

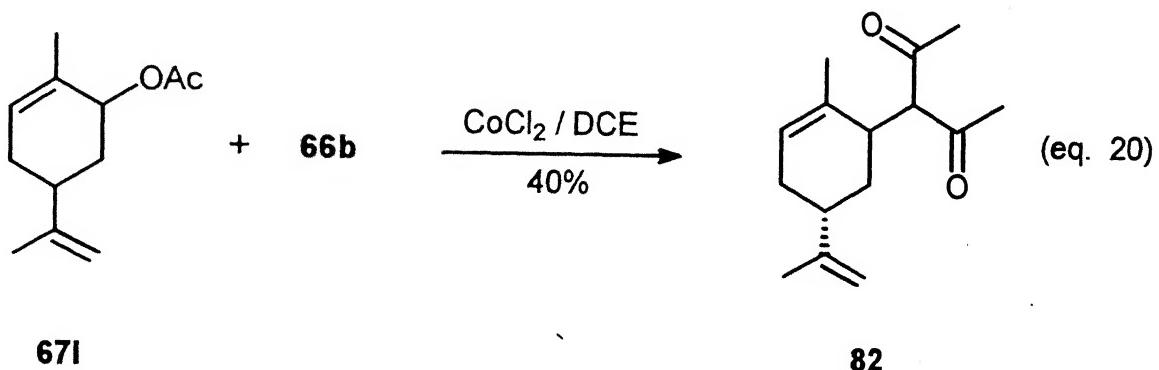




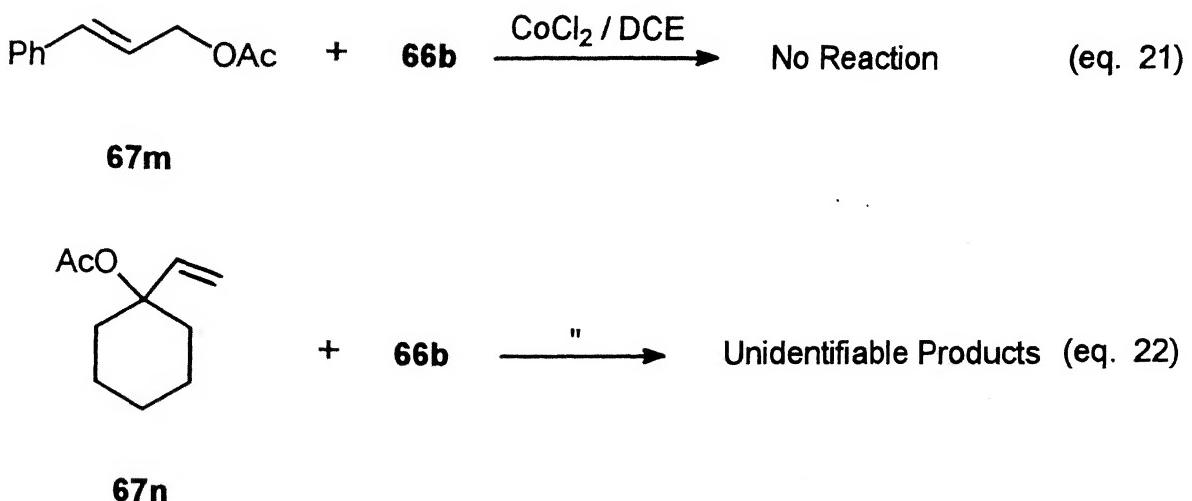
surprisingly the major regioisomer **81** does not have the extensive conjugation between phenyl ring, triple bond and double bond (eq. 19). Interestingly, the major regioisomer was found to have trans double bond geometry. A diastereomeric mixture of carvoyl acetate **67l** also reacts with acetylacetone to afford the trans diastereomer **82** as the only product which does not



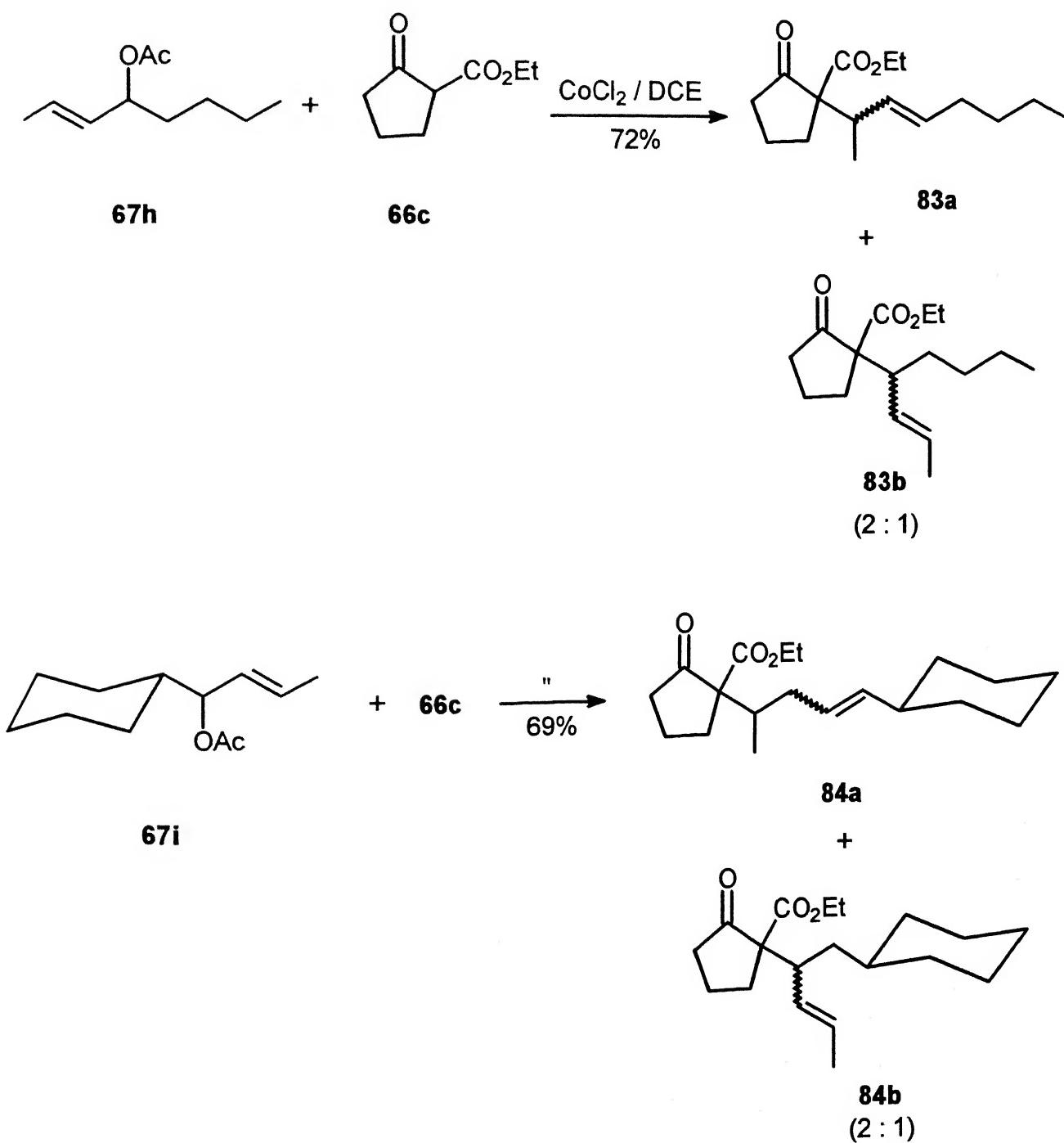
show any optical activity when subjected to polarimeter examination (eq. 20). It is interesting to note that acetylacetone does not react with primary acetate **67m** under these conditions and the latter is mainly recovered unchanged.



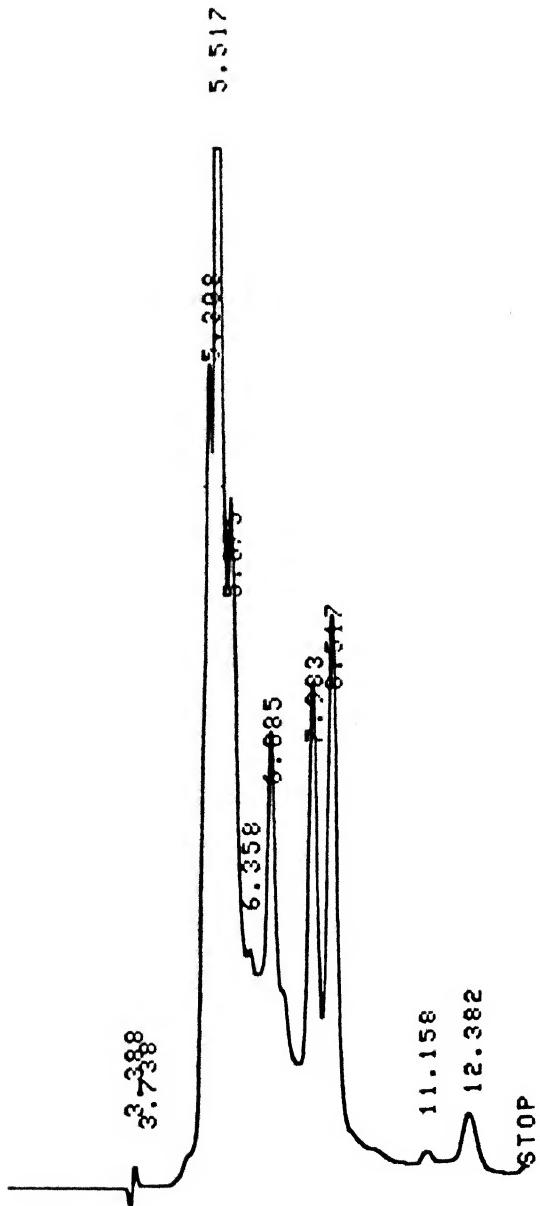
On the other hand, monosubstituted tertiary acetate **67n** gives a mixture of unidentifiable products along with some oligomers (eq. 21, 22).



The cyclic ketoester also reacts with a variety of allylacetates to afford the corresponding allylated products in good yields. Thus the reaction of allylacetates **67h** and **67i** with ethyl 2-oxo-cyclopentanecarboxylate **66c** provides a mixture of regioisomers **83a-b** and **84a-b** respectively where one of the regioisomer is slightly in excess over the other (Scheme 3.17). Once again, they were obtained as a mixture (1:1) of geometrical isomers. Suitable manipulation of conditions did not alter this regiosomeric ratio. The ratio of these isomers is obtained by HPLC analysis on the crude reaction mixture and as seen from the HPLC diagram, a mixture of four diastereomers obtained in which one of the diastereomer appears to be major.

**Scheme 3.17**

C. ART  
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DEPT. OF CHEMISTRY  
I.I.T. KANPUR



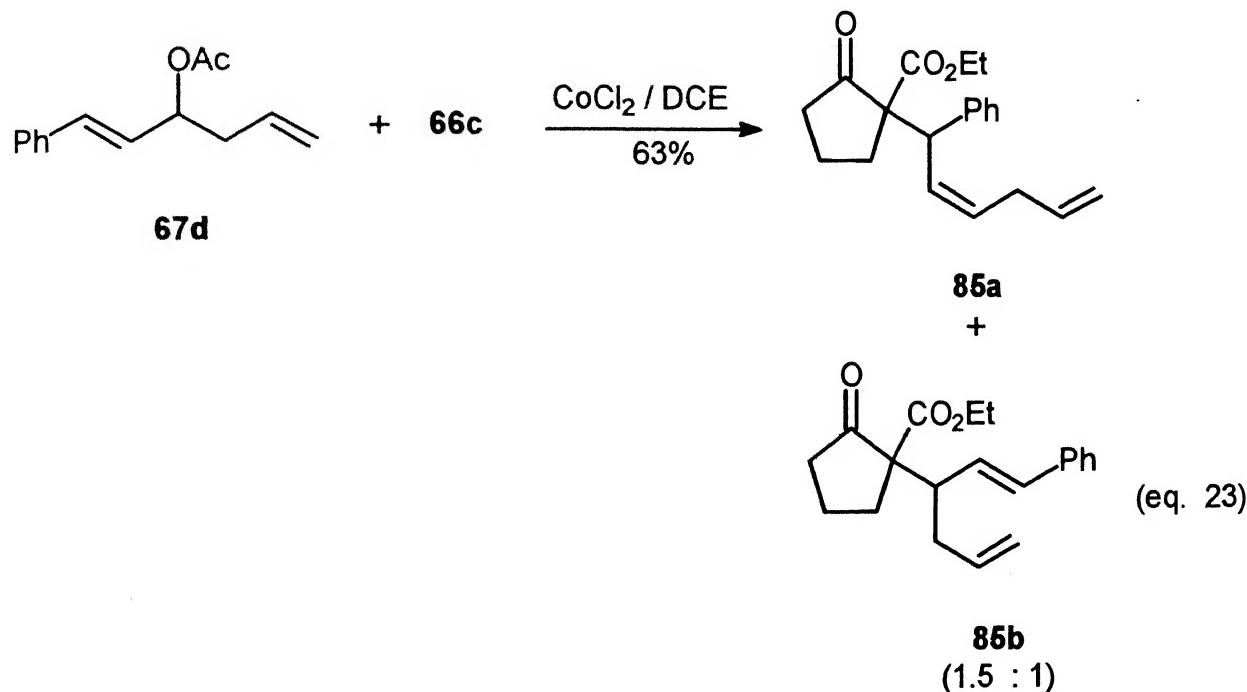
## CHROMATOGRAM 1 MEMORIZED

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SAMPLE NO 0  
REPORT NO 103

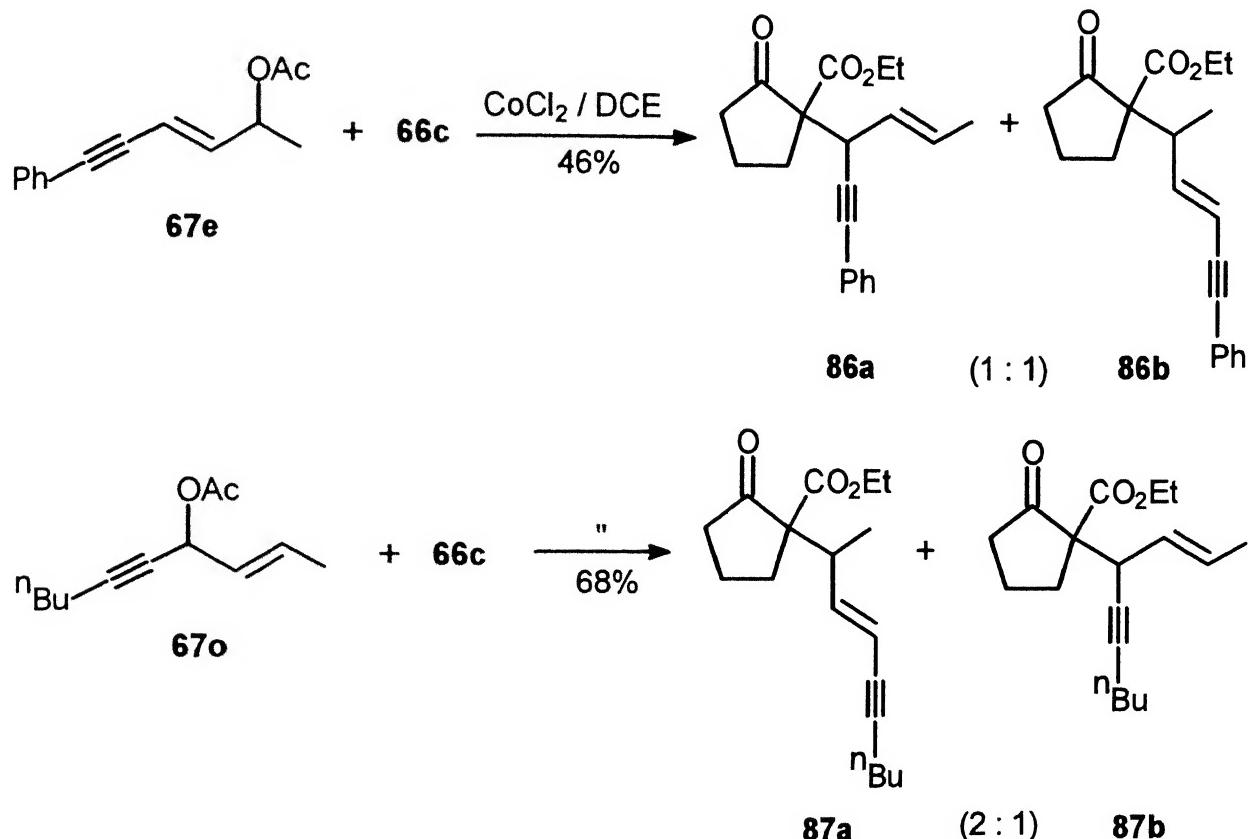
FILE 2  
METHOD 41

PKNO	TIME	AREA	WK	IDNO	CONC	NAME
1	5.308	105283			14.992	
2	5.517	191719	V		27.3001	
3	5.875	98433	V		14.0165	
4	6.885	110397	V		15.7202	
5	7.983	81534	V		11.6101	
6	8.517	114898	SY		16.361	
TOTAL		702263			100	

Ethyl 2-oxo- cyclopentanecarboxylate **66c** also reacts with the diene acetate **67d** to give a mixture of diastereomers and regioisomers **85a-b**. One of the regioisomer **85a** appears to be slightly in excess over the other (eq. 23). However; the geometry of the double bond was

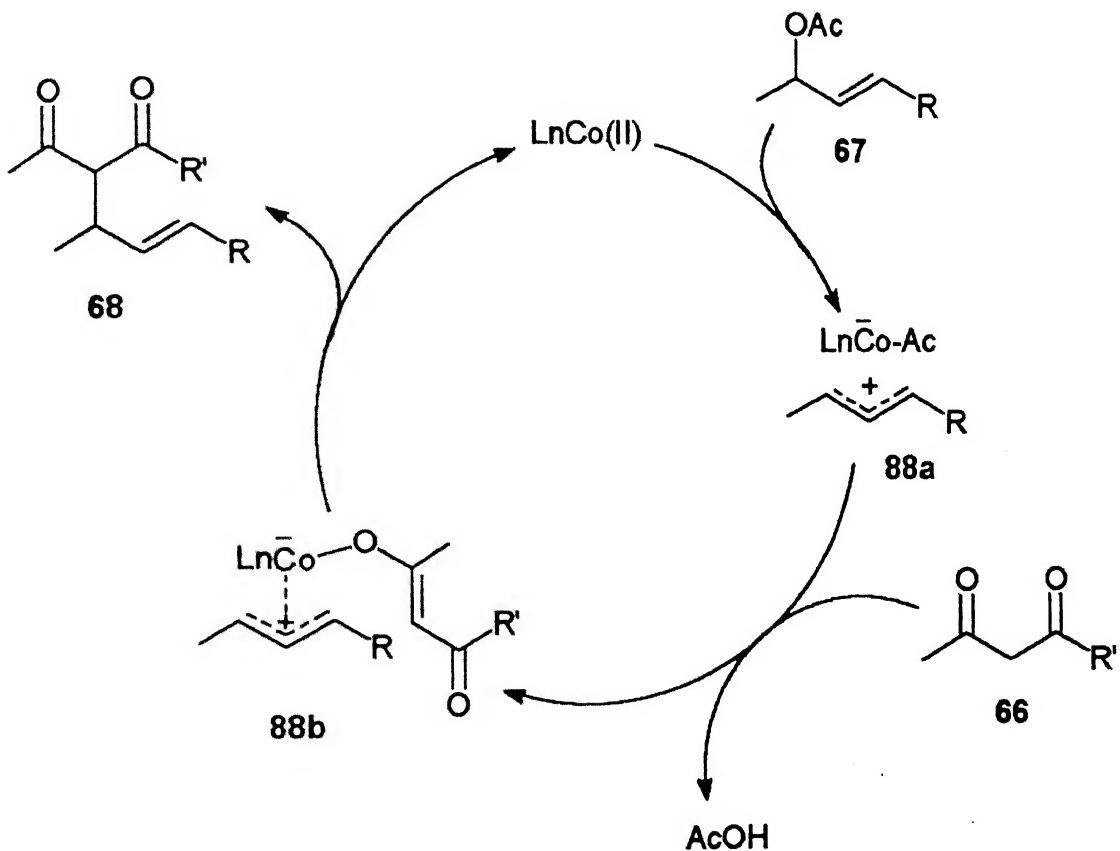


found to be E- in the case of both regioisomers. It is interesting to note that the conjugation between the double bond and phenyl ring once again has been disrupted during this reaction. **66c** also reacts with the dienylacetates **67e** and **67o** to provide a mixture of regio- and diastereo isomers **86a-b** and **87a-b** respectively (Scheme 3.18). The dienyl acetate **67e** provides an equal mixture of regioisomers whereas, **67o** affords the branched and linear alkylated products **87a** and **87b** in a ratio of 2:1. The preference for selectivity in the case of acetate **67o** is not clear. It is worth noting that the reaction with ethyl 2-oxo-cyclopentanecarboxylate is much faster than methylacetoacetate.

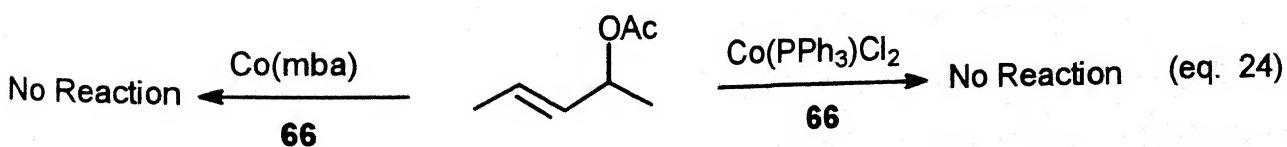
**Scheme 3.18**

## MECHANISM

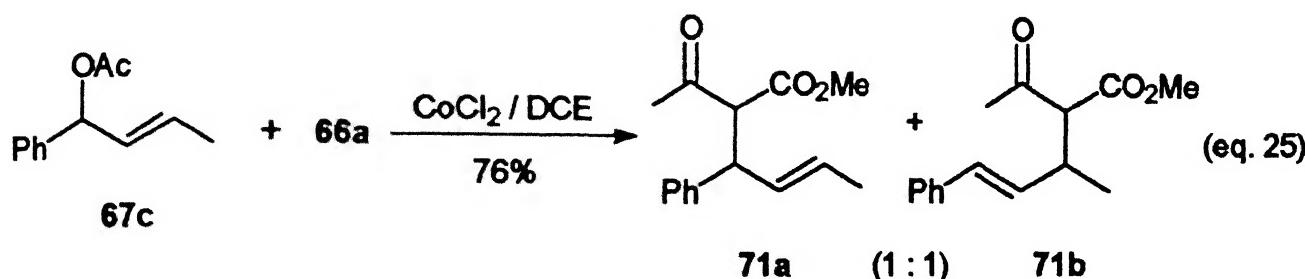
The mechanism of these reactions may be analogous to the palladium or molybdenum catalyzed reactions. We have already proposed in the chapter 1 that the allylacetate may form a cobalt  $\pi$ -allyl complex on interaction with cobalt chloride. Thus, it is conceivable that the present reaction is initiated by the formation of a cobalt  $\pi$ -allyl complex **88a** from allylacetate **67**. The formation of such a complex **88a** will perhaps result due to the initial coordination of the metal with double bond which results into the weakening of allylic carbon-oxygen bond subsequent to coordination of carbonyl oxygen with the metal (Scheme 3.19). This kind of complex formation is already well known in the case of palladium and

**Scheme 3.19**

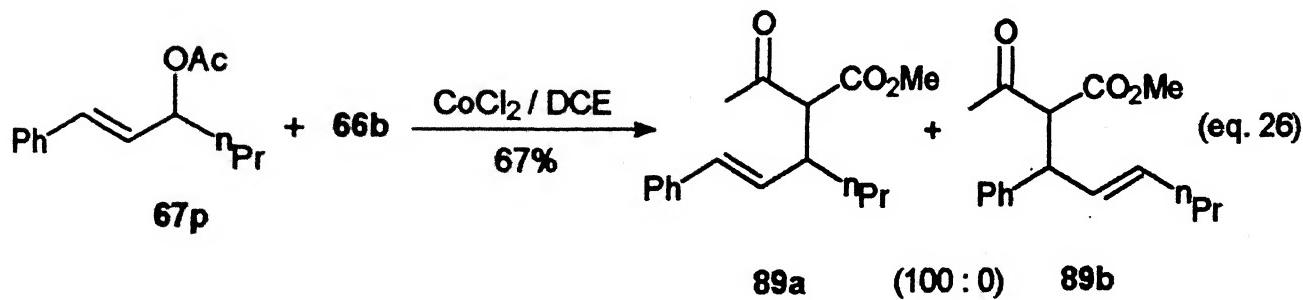
other metals. Initial coordination of cobalt with the double bond requires cobalt to behave like a Lewis acid which subsequently results into the ionization of allylacetate. This realisation is born by the fact that if electron rich ligand is attached to cobalt chloride then the allylacetate remains unreactive. Thus the addition of a small amount of triphenylphosphine or the schiff base ligand completely inhibits the ionization of allyl acetate (eq. 24). These observations clearly support the assumption that cobalt chloride is behaving like a good Lewis acid towards



the ionization of allylacetate. The formation of a free allyl cation is ruled out here because no side products (like elimination etc.) were observed under these conditions. Moreover, if a free allyl cation is formed then the reaction with acetate **67c** should result into the formation of product **71a** predominantly (eq. 25), however, this is not found to be the case. Similarly,

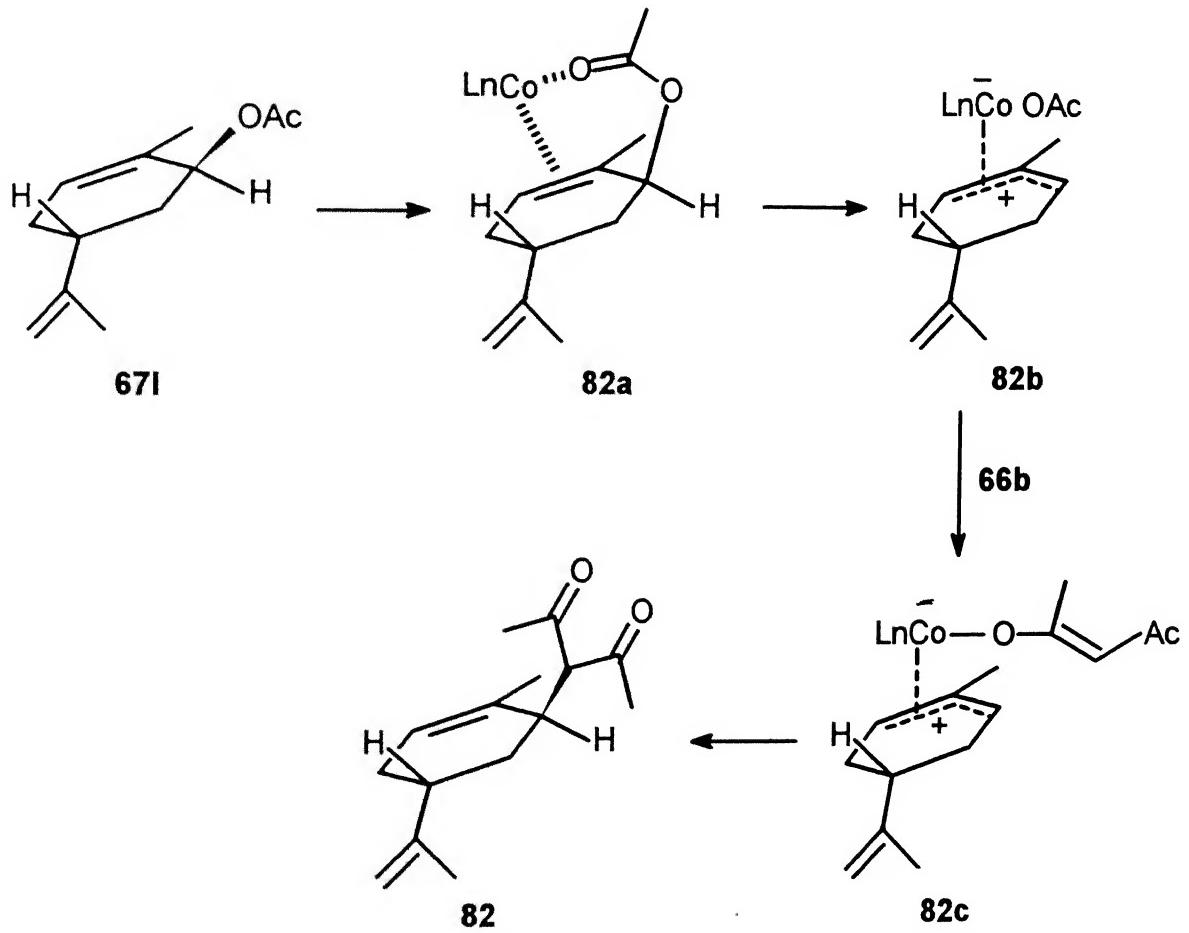


the reaction of allylacetate **67p** with acetylacetone **66b** should have given the product **89b** instead of **89a** as the major product (eq. 26). Because, the product **89b** should have arisen



from a more stable benzylic cation. This reaction is governed by steric factors and this observation clearly supports that free allyl cation is unlikely to be the reacting species. Also the formation of mixture of regioisomers is indicative of the fact that if free allyl cation were to be formed then the ratio of these isomers would have been unequal, particularly in reactions with ethyl 2-oxo-cyclopentanecarboxylate **66c** and allylacetates. However, we do not have a direct evidence for the involvement of a  $\pi$ -allyl complex but the formation of clean products and the absence of any cyclized products from diene and dienylacetate clearly supports that a free allyl cation is not formed during these reactions. Thus, the reaction of acetylacetone with carvoyl acetate **67l** give rise to only the anti diastereomer **82** and this result indicates that a  $\pi$ -allyl cobalt complex **82b** may be involved during this

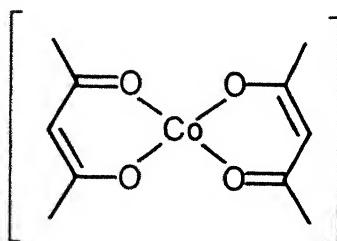
scheme 3.20. Thus the anti-acetate **67l** will give rise to anti  $\pi$ -allyl complex **82b** which will react with 1,3-dicarbonyl compound **66b** via a redox process to form a cobalt enolate **82c**. The latter species may undergo an intramolecular carbon-carbon bond formation to afford the allylated product **82**. We have earlier proposed (chapter 2) a cobalt-enolate from 1,3-



**Scheme 3.20**

dicarbonyl compound. The high regioselectivity in the case of acetylacetone, which will easily form a stable enolate, may be arising due to this intramolecular reaction. Thus these reactions may be proceeding via an initial coordination of the  $\pi$ -bond which will subsequently result into the formation of  $\pi$ -allyl complex. The initial coordination of cobalt to the double bond is an important and necessary step because we have seen that acetates with no double bond are completely unreactive under these conditions. Similarly, the reaction with benzylic acetate

fails to provide any benzylic cation under these conditions. These observations also support the formation of  $\pi$ -allyl complex. Further, it appears that the reaction with acetylacetone is catalyzed by the *in situ* generated  $\text{Co}(\text{acac})_2$  90 instead of  $\text{CoCl}_2$ .



90

In conclusion, this chapter has described a useful procedure for the allylation of 1,3-dicarbonyl compounds catalyzed by cobalt(II) chloride. This methodology seems to be operationally simple and efficient to the existing similar transformation. Advantage of this methodology is that it does not require the formation of an enolate of a 1,3-dicarbonyl compound. It also utilizes cobalt(II) chloride which is cheaper than palladium or molybdenum complexes. Although the regioselectivity is not high, but the suitable modification of reaction conditions may result in the improvement of selectivity. Further endeavours in this direction will address regiochemical and functional groups compatibility issues in these reactions. This preliminary study has clearly highlighted that cobalt catalyzed allylation is a formidable alternative to similar known transformations.

### 3.3 EXPERIMENTAL

#### Materials and Methods

1,2-Dichloroethane, THF and ether were purified by standard procedure. Acetylacetone, methyl acetoacetate, alkyl halides and aldehydes were purchased commercially and purified prior to use.  $\text{CoCl}_2$  was purchased from LOBA India Ltd., Bombay and dried at  $120^\circ\text{C}$  for 2-3 h before the reaction. Column chromatography was performed by using ACME silica gel (60-120 mesh).  $^1\text{H-NMR}$  spectra were recorded at 60, 80 and 400 MHz in  $\text{CDCl}_3$  or  $\text{CCl}_4$ . Elemental analysis was conducted using Coleman automatic C, H and N analyzer. All the known compounds were characterised by comparing the data from the literature.

#### General Procedure for the Synthesis of Allylacetates

Alcohols were prepared either by  $\text{NaBH}_4$  reduction of corresponding carbonyl compounds or by the reaction of Grignard reagent with the corresponding carbonyl compounds or by the reaction of allyl bromide with  $\alpha, \beta$ -unsaturated aldehydes<sup>52</sup>. These alcohols were acylated with acetic anhydride and triethylamine in the presence of 4-N,N-dimethylamino pyridine<sup>53</sup>. Preparation of some of the representative examples are given below.

#### Allylacetate 67d<sup>54</sup>

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.05 (s, 5H), 6.65-5.9 (m, 2H), 5.9-5.2 (m, 2H), 5.2-4.7 (m, 2H), 2.4 (t,  $J = 8$  Hz, 2H), 1.95 (s, 3H).

#### Allylacetate 67i

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  5.8-5.1 (m, 2H), 5.05-4.6 (dd,  $J = 12$  and 4 Hz, 1H), 1.9 (s, 3H), 1.6 (d,  $J = 6$  Hz, 3H), 1.6-0.75 (m, 11H).

#### Allylacetate 67o

To a solution of 1-hexyne (1 mol equiv.) in dry THF, n-butyl lithium (1.2 mol equiv.) was added at  $\sim -20^\circ\text{C}$ . Reaction mixture was stirred at room temperature for 0.5 h at this temperature and then stirred at room temperature for 0.5 h. A THF solution of crotonaldehyde (1.2 mol equiv.) was added dropwise to the reaction mixture at  $0^\circ\text{C}$  and stirred for 1 h and

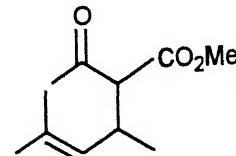
then warmed to ~50° C. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution and extracted with ethyl acetate (3x50 mL). The organic layer was washed with saturated NH<sub>4</sub>Cl solution and brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the alcohol which was acylated with acetic anhydride and triethylamine in the presence of DMAP. This acetate was purified by column chromatography on silica gel.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 5.85-5.3 (m, 2H), 2.4-2.0 (m, 2H), 1.95 (s, 3H), 1.7 (d, J = 7 Hz, 3H), 1.55-1.05 (m, 4H), 0.9 (t, 3H).

### General Procedure for Allylation of 1,3-Dicarbonyl Compounds with Allylacetates

Allyl acetate (5 mmol) and 1,3-dicarbonyl compound (5 mmol) were heated at 70° C while stirring in 1,2-dichloroethane (30 mL) in the presence of catalytic amount of dry cobalt(II) chloride (~30 mg) for 8-12 h. Removal of solvent gave a residue which was taken into ethyl acetate and washed successively with saturated solution of sodium bicarbonate (3x25 mL), water (2x20 mL) and brine (1x25 mL). Drying (MgSO<sub>4</sub>) and evaporation of solvent gave a residue which was chromatographed over silica gel to give the products as a mixture of two regioisomers.

Methyl 2-acetyl 3,5-dimethyl hex-4-enoate 69a



The reaction was performed as described above with the allyl acetate 67a (1.22 g, 8.6 mmol), methyl acetoacetate (1.2 g, 10.3 mmol) in the presence of catalytic amount of CoCl<sub>2</sub> (~30 mg) in dry 1,2-dichloroethane (30 mL). Purification by column chromatography afforded 69a (0.46 g, 27%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 5.45-5.2 (m, 1H), 4.9-4.55 (m, 1H), 3.6 (s, 3H), 3.2-2.9 (m, 1H), 2.0 (s, 3H), 1.6 (s, 6H), 0.9 (m, 3H).

IR (Thin film) : ν<sub>max</sub> 3030, 1740, 1700, 1430 cm<sup>-1</sup>.

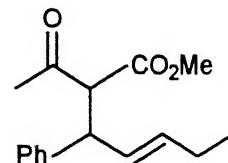
Anal. Calcd. for  $C_{11}H_{18}O_3$  : C, 66.68; H, 9.08

Found : C, 66.74; H, 9.11.

### Compound 70a and 70b

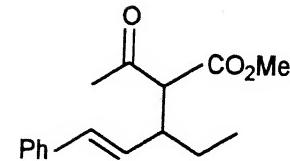
Allyl acetate **67b** (1.02 g, 5 mmol), methyl acetoacetate (0.7 g, 6 mmol) and  $CoCl_2$  ( $\sim$ 30 mg) in dry 1,2-dichloroethane (30 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded (0.71 g, 55%) as a mixture of two regioisomers.

**Methyl 2-acetyl 3-phenyl hept-4-enoate 70a**



<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  7.0 (s, 5H), 5.4 (m, 2H), 3.8 (m, 2H), 3.6 (s, 3H), 2.2 (s, 3H), 1.9 (m, 2H), 1.0 (t, J = 7 Hz, 3H).

**Methyl 2-acetyl 3-ethyl 5-phenyl pent-4-enoate 70b**



<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  7.0 (s, 5H), 6.3 (d, J = 16 Hz, 1H), 6.0-5.6 (m, 1H), 3.5 (s, 3H), 3.35 (m, 1H), 3.1-2.5 (m, 1H), 1.9 (s, 3H), 1.6-1.2 (m, 2H), 1.0 (t, J = 7 Hz, 3H).

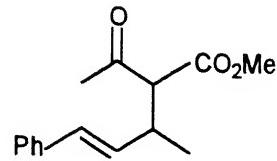
IR (Thin film) :  $\nu_{max}$  3040, 1730, 1700,  $cm^{-1}$ .

Anal. Calcd. for  $C_{16}H_{20}O_3$  : C, 73.88; H, 7.69

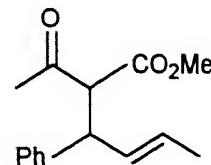
Found : C, 73. 92; H, 7.72.

### Compound 71a and 71b

The reaction was performed as described above with **67c** (1.0 g, 5.26 mmol) methyl acetoacetate (0.91 g, 7.9 mmol) in the presence of catalytic amount of  $CoCl_2$  ( $\sim$ 30 mg) in dry 1,2-dichloroethane (30 mL). Purification by column chromatography afforded (0.98 g, 76%) as a mixture of two regioisomers.

**Methyl 2-acetyl 3-methyl 5-phenyl pent-4-enoate 71a**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.05 (s, 5H), 6.3 (d, J = 16 Hz, 1H), 6.1-5.75 (m, 1H), 3.5 (s, 3H), 3.3 (m, 1H), 3.1-2.8 (m, 1H), 2.0 (s, 3H), 1.1 (d, J = 7 Hz, 3H).

**Methyl 2-acetyl 3-phenyl hex-4-enoate 71b**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.0 (s, 5H), 5.4-5.2 (m, 2H), 3.75 (m, 2H), 3.6 (s, 3H), 2.1 (s, 3H), 1.55 (d, J = 4 Hz, 3H).

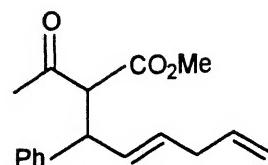
IR (Thin film) : ν<sub>max</sub> 3040, 1740, 1710 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub> : C, 73.19; H, 7.31.

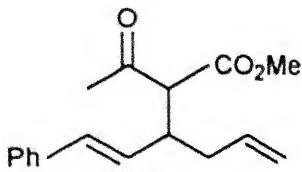
Found : C, 73.26; H, 7.35.

**Compound 72a and 72b**

The reaction was performed as described above with the allyl acetate 67d (1.3 g, 6 mmol), methyl acetoacetate (0.83 g, 7.2 mmol) and catalytic amount of CoCl<sub>2</sub> (~30 mg) in 1,2-dichloroethane (30 mL). Purification by column chromatography afforded (0.85 g, 52%) as a mixture of two regioisomers.

**Methyl 2-acetyl 3-phenyl octa-4,7-dienoate 72a**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.28 (s, 5H), 5.9-5.4 (m, 3H), 5.25-4.78 (m, 2H), 4.05 (m, 2H), 3.75 (s, 3H), 2.85 (m, 2H), 2.31 (s, 3H).

**Compound 72b**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.3 (s, 5H), 6.5 (d, J = 18 Hz, 1H), 6.28-5.90 (m, 1H), 5.25-4.75 (m, 3H), 3.72 (s, 3H), 3.5 (d, J = 7 Hz, 1H), 3.32-2.95 (m, 1H), 2.3 (m, 2H), 2.2 (s, 3H).

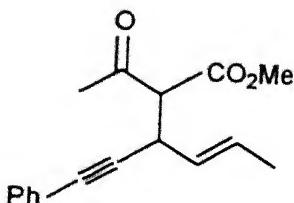
IR (Thin film) : ν<sub>max</sub> 3040, 1740, 1715, 1490, 1450, 1430, 1350 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>17</sub>H<sub>20</sub>O<sub>3</sub> : C, 75.01; H, 7.35.

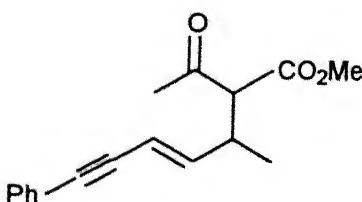
Found : C, 75.08; H, 7.39.

### Compound 73a and 73b

Allyl acetate **67e** (0.7 g, 3.27 mmol), methyl acetoacetate (0.45 g, 3.9 mmol) and CoCl<sub>2</sub> (~30 mg) were heated to 80° C in 1,2-dichloroethane (30 mL) to afford (0.28 g, 32%) as a mixture of two regioisomers.

**Compound 73a**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.35 (s, 5H), 6.2-5.3 (m, 2H), 4.05 (m, 1H), 3.75 (s, 3H), 3.68 (d, J = 5.0 Hz, 1H), 2.4 (s, 3H), 1.72 (d, J = 7.5 Hz, 3H).

**Compound 73b**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.3 (s, 5H), 6.05 (dd, J = 4 and 18 Hz, 1H), 5.85 (d, J = 18 Hz, 1H), 3.80 (s, 3H), 3.48 (d, J = 7.5 Hz, 1H), 3.15 (m, 1H), 2.18 (s, 3H), 1.05 (d, J = 7.0 Hz, 3H).

IR (Thin film) : ν<sub>max</sub> 2200, 1740, 1700, 1585, 1480, 1430, 1250 cm<sup>-1</sup>.

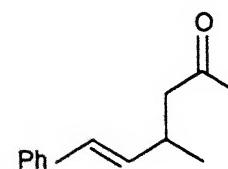
Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>3</sub> : C, 75.57; H, 6.66.

Found : C, 75.63; H, 6.70.

### Compound 74a and 74b

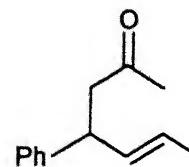
Compound 70a (0.29 g, 1.17 mmol), Potassium carbonate (0.20 g, 1.5 mmol) in dry ethanol (30 mL) were heated to 85° C for 15 h. Removal of solvent gave a residue which was taken into ethyl acetate and washed with water (3x30 mL). Drying ( $\text{MgSO}_4$ ) and evaporation of solvent afforded (0.19 g, 89%) as a mixture of two regioisomers.

**4-Methyl 6-phenyl hex-5-ene-2-one 74a**



$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  6.9 (s, 5H), 6.2-5.85 (m, 2H), 3.0-2.25 (m, 3H), 1.9 (s, 3H), 1.1 (d,  $J = 8$  Hz, 3H).

**4-Phenyl hept-5-ene-2-one 74b**



$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  6.95 (s, 5H), 5.3 (m, 2H), 4.0-3.5 (m, 1H), 3.0-2.5 (m, 2H), 2.0 (s, 3H), 1.6 (d,  $J = 4$  Hz, 3H).

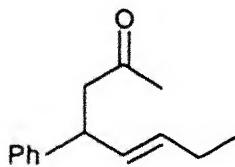
IR (Thin film) :  $\nu_{max}$  3060, 1700, 1585, 1480, 1350, 1150  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}\text{O}$  : C, 82.99; H, 8.50

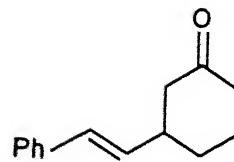
Found : C, 83.12; H, 8.59.

### Compound 75a and 75b

Compound 71 (0.17 g, 0.65 mmol), Potassium carbonate (0.13 g, 1 mmol) in dry ethanol (20 mL) were subjected to the reaction conditions ad described above to afford (0.12 g, 91%) as a mixture of two regioisomers.

**4-Phenyl oct-5-ene-2-one 75a**

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 6.9 (s, 5H), 5.25 (m, 2H), 4.0-3.45 (m, 1H), 2.6 (d, J = 7 Hz, 2H), 1.8 (s, 3H), 1.5-1.3 (m, 2H), 0.9 (t, J = 7 Hz, 3H).

**4-Ethyl 6-phenyl hex-5-ene-2-one 75b**

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 6.95 (s, 5H), 6.3 (d, J = 16 Hz, 1H), 6.0-5.6 (m, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 1.9 (s, 3H), 1.2 (m, 2H), 0.8 (t, J = 7 Hz, 3H).

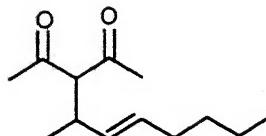
IR (Thin film) : ν<sub>max</sub> 3030, 1710, 1590, 1490, 1350, 1150 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>O : C, 83.18; H, 8.90

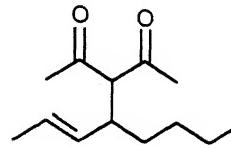
Found : C, 83.24; H, 8.95.

**Compound 76a and 76b**

Allyl acetate **67h** (0.61 g, 3.6 mmol) and acetylacetone (0.43 g, 4.3 mmol) were heated at 70° C in 1,2-dichloroethane (30 mL) in the presence of cobalt(II) chloride (~30 mg) for 8 h. The usual workup followed by column chromatography afforded (0.29 g, 38%) as a mixture of two regioisomers.

**3-Acetyl 4-methyl dec-5-ene-2-one 76a**

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 5.6-5.05 (m, 2H), 3.35 (d, J = 4.0 Hz, 1H), 3.1-2.7 (m, 1H), 2.3-2.15 (m, 2H), 2.1 (s, 3H), 2.0 (s, 3H), 1.5-1.1 (m, 4H), 0.95 (d, J = 7.0 Hz, 6H).

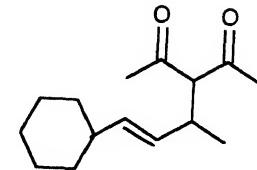
**3-Acetyl 4-butyl-hept-5-ene-2-one 76b**

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 5.6-5.05 (m, 2H), 3.5 (d, J = 4.0 Hz, 1H), 3.1-2.7 (m, 1H), 2.1 (s, 3H), 2.0 (s, 3H), 1.65 (d, J = 7 Hz, 3H), 1.5-0.9 (m, 9H).

IR (Thin film) : ν<sub>max</sub> 2980, 2960, 1710, 1690, 1350 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>13</sub>H<sub>22</sub>O<sub>2</sub> : C, 74.30; H, 10.47.

Found : C, 74.43; H, 10.51.

**3-Acetyl 4-methyl 6-cyclohexyl hex-5-ene-2-one 77**

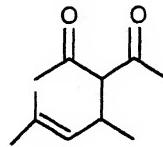
Allyl acetate 67i (1.18 g, 6 mmol) acetylacetone (0.7 g, 7 mmol) and CoCl<sub>2</sub> (~30 mg) were heated to 80° C in 1,2-dichloroethane (30 mL) to afford 77 (0.68 g, 48%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 5.37-5.12 (m, 2H), 3.53 (d, J = 12.5 Hz, 1H), 3.1-2.8 (m, 1H), 2.1 (s, 3H), 2.0 (s, 3H), 1.9-1.34 (m, 5H), 1.31-1.0 (m, 6H), 0.9 (d, J = 6.25 Hz, 3H).

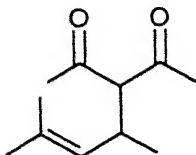
IR (Thin film) : ν<sub>max</sub> 1720, 1690, 1350 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub> : C, 76.28; H, 10.16.

Found : C, 76.39; H, 10.23.

**3-Acetyl 4,6-dimethyl hept-5-ene-2-one 78**

Allyl acetate 67a (1.2 g, 8.4 mmol), acetylacetone (1.01 g, 10 mmol) and CoCl<sub>2</sub> (~30 mg) in 1,2-dichloroethane (30 mL) were subjected to the reaction conditions as described above. The usual workup followed by purification using column chromatography afforded 78 (0.54 g, 35%).

**Compound 78**

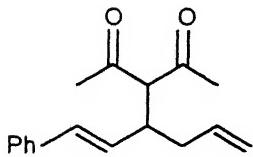
This compound was prepared as described above by the reaction of allyl acetate **67j** (0.88 g, 6.2 mmol), acetylacetone (0.74 g, 7.4 mmol) and dry  $\text{CoCl}_2$  ( $\sim$ 30 mg) in 1,2-dichloroethane (30 mL) at  $85^\circ\text{C}$  for 6 h to give **78** (0.61 g, 54%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  4.9 (d,  $J = 10$  Hz, 1H), 3.59 (d,  $J = 12.5$  Hz, 1H), 3.47-3.21 (m, 1H), 2.19 (s, 3H), 2.05 (s, 3H), 1.69 (s, 6H), 0.9 (d,  $J = 7.5$  Hz, 3H).

IR (Thin film) :  $\nu_{max}$  1710, 1690  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{18}\text{O}_2$  : C, 72.54; H, 9.88.

Found : C, 72.67; H, 9.92.

**Compound 79**

Allyl acetate **67d** (1.4g, 6.8 mmol), acetylacetone (0.82 g, 8.2 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) were heated to  $80^\circ\text{C}$  in 1,2-dichloroethane (30 mL) to afford **79** (1.11 g, 64%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  7.05 (s, 5H), 6.15 (d,  $J = 16$  Hz, 1H), 5.62 (dd,  $J = 16$  and 8 Hz, 1H), 5.30 (m, 1H), 4.92 (br s, 1H), 4.75 (m, 1H), 3.50 (d,  $J = 10$  Hz, 1H), 2.91 (m, 1H), 2.10 (m, 2H), 2.0 (s, 3H), 1.90 (s, 3H).

IR (Thin film) :  $\nu_{max}$  3080, 1720, 1690, 1350  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}_2$  : C, 79.70; H, 7.80.

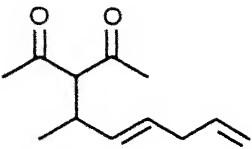
Found : C, 79.79; H, 7.85.

### Compound 80a and 80b

Allyl acetate **67k** (0.82 g, 5.3 mmol) and acetylacetone (0.64 g, 6.4 mmol) were heated at  $70^\circ\text{C}$  in 1,2-dichloroethane (30 mL) in the presence of cobalt(II) chloride ( $\sim$ 30 mg) for 9 h. The usual workup followed by column chromatography afforded (0.29 g, 26%) as a mixture

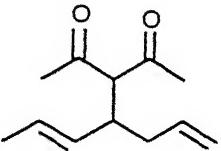
of two regioisomers.

**Compound 80a**



<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 5.78-5.25 (m, 3H), 5.15-4.84 (m, 2H), 3.65 (d, J = 10 Hz, 1H), 3.22-2.87 (m, 1H), 2.75 (t, J = 5 Hz, 2H), 2.2 (s, 3H), 2.1 (s, 3H), 1.0 (d, J = 6.25 Hz, 3H).

**Compound 80b**



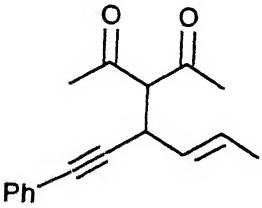
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 5.78-5.25 (m, 3H), 5.15-4.84 (m, 2H), 3.65 (d, J = 10 Hz, 1H), 3.22-2.87 (m, 1H), 2.2 (s, 3H), 2.1 (s, 3H), 1.69 (t, J = 5 Hz, 2H), 1.3 (d, J = 6.25 Hz, 3H).

IR (Thin film) : ν<sub>max</sub> 3080, 1720, 1690, 1350 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>18</sub>O<sub>2</sub> : C, 74.24; H, 9.27.

Found : C, 74.31; H, 9.36.

**Compound 81**



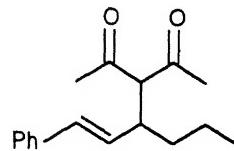
This compound was prepared from the reaction of allyl acetate **67e** (0.39 g, 1.82 mmol), acetylacetone (0.21 g, 2.18 mmol) and CoCl<sub>2</sub> (~20 mg) in dry 1,2-dichloroethane (30 mL) in 55% (0.25 g) yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.3 (s, 5H), 6.0-5.62 (m, 1H), 5.5-5.15 (m, 1H), 4.19-3.75 (m, 2H), 2.25 (s, 3H), 2.15 (s, 3H), 1.75 (d, J = 7.5 Hz, 3H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 3080, 2160, 1720, 1690 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>2</sub> : C, 80.33; H, 7.08.

Found : C, 80.39; H, 7.12.

**3-Acetyl 4- propyl 6-phenyl hex-5-ene-2-one 89a**

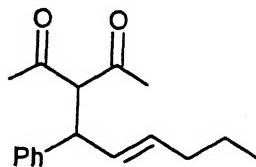
This compound was prepared, as described above by the reaction of allyl acetate **67p** (0.95 g, 4.36 mmol), acetylacetone (0.52 g, 5.23 mmol) and dry CoCl<sub>2</sub> (~30 mg) in dry 1,2-dichloroethane (30 mL). Purification by column chromatography (silica gel, 8% EtoAc in hexane) afforded **89a** in 53% (0.6 g) yield.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.1 (s, 5H), 6.25 (d, J = 16 Hz, 1H), 5.6 (dd, J = 16 and 8 Hz, 1H), 3.6 (d, J = 10 Hz, 1H), 3.2-2.6 (m, 1H), 2.15 (s, 3H), 2.0 (s, 3H), 1.3 (m, 4H), 0.9 (t, J = 6 Hz, 3H).

IR (Thin film) : ν<sub>max</sub> 3020, 1710, 1690, 1350 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>17</sub>H<sub>22</sub>O<sub>2</sub> : C, 79.08; H, 8.52.

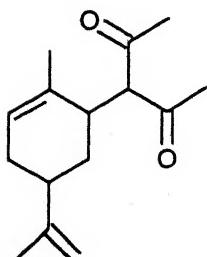
Found : C, 79.23; H, 8.56.

**3-Acetyl 4-phenyl non-5-ene-2-one 89b**

This compound was isolated from the reaction mixture as described for **89a** in 14% (0.15 g) yield.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) : δ 7.0 (s, 5H), 5.45-5.15 (m, 2H), 3.95 (m, 2H), 2.05 (s, 3H), 2.0-1.75 (m, 2H), 1.7 (s, 3H), 1.65-1.01 (m, 2H), 0.85 (t, J = 6.0 Hz, 3H).

IR (CCl<sub>4</sub>) : ν<sub>max</sub> 3020, 1710, 1690 cm<sup>-1</sup>.

**Compound 82**

acetylacetone (0.6 g, 6 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in dry 1,2-dichloroethane. Purification by column chromatography (silica gel, 8% EtoAc in hexane) afforded **82** (0.47 g, 40%).

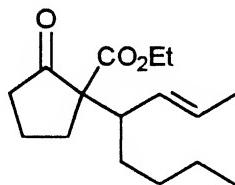
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  5.5 (br s, 1H), 4.62 (s, 2H), 3.9 (d,  $J = 8$  Hz, 1H), 2.95 (m, 1H), 2.3-1.85 (m, 8H), 1.72-1.4 (m, 9H).

IR (Thin film) :  $\nu_{max}$  1710, 1700  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_2$  : C, 76.94; H, 9.39.

Found : C, 77.02; H, 9.44.

Compound **83**



The reaction was performed as described above with the allyl acetate **67h** (0.82 g, 4.8 mmol), ethyl 2-oxo-cyclopentane carboxylate (0.9 g, 5.7 mmol) and catalytic amount of  $\text{CoCl}_2$  ( $\sim$ 30 mg) in 1,2-dichloroethane (30 mL). Purification by column chromatography afforded **83** (0.92 g, 72%).

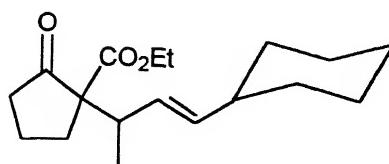
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  5.4-4.9 (m, 2H), 4.0 (q,  $J = 7.5$  Hz, 2H), 3.0 (m, 1H), 2.4-1.7 (m, 6H), 1.55 (d,  $J = 6$  Hz, 3H), 1.4-1.0 (m, 6H), 0.9 (m, 6H).

IR ( $\text{CCl}_4$ ) :  $\nu_{max}$  1740, 1720  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{16}\text{H}_{26}\text{O}_3$  : C, 72.19; H, 9.77

Found : C, 72.25; H, 9.82.

Compound **84**



This compound was prepared as described above by the reaction of allyl acetate **67i** (1.36 g, 7.3 mmol), ethyl 2-oxo-cyclopentane carboxylate (1.14 g, 7.3 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in 1,2-dichloroethane (30 mL) at 85° C for 8 h to give **84** (1.47 g, 69%).

tion conditions as described above. The usual workup followed by column chromatography afforded **86** (0.30 g, 46%) as a mixture of two regioisomers.

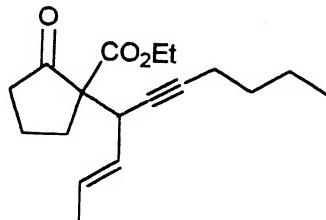
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) :  $\delta$  7.3 (s, 5H), 6.12-5.62 (m, 1H), 5.53-5.16 (m, 1H), 4.35-4.0 (m, 3H), 2.78-1.78 (m, 6H), 1.65 (d, J = 6.25 Hz, 3H), 1.22 (t, J = 6.25 Hz, 3H).

IR (Thin film) :  $\nu_{max}$  3080, 2200, 1750, 1720 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>20</sub>H<sub>22</sub>O<sub>3</sub> : C, 77.43; H, 7.09

Found : C, 77.51; H, 7.16.

Compound 87



Allyl acetate **67o** (0.97 g, 5 mmol), ethyl 2-oxo-cyclopentane carboxylate (1.0 g, 7 mmol) and CoCl<sub>2</sub> (~30 mg) in dry 1,2-dichloroethane (30 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **87** (0.99 g, 68%) as a mixture of two regioisomers.

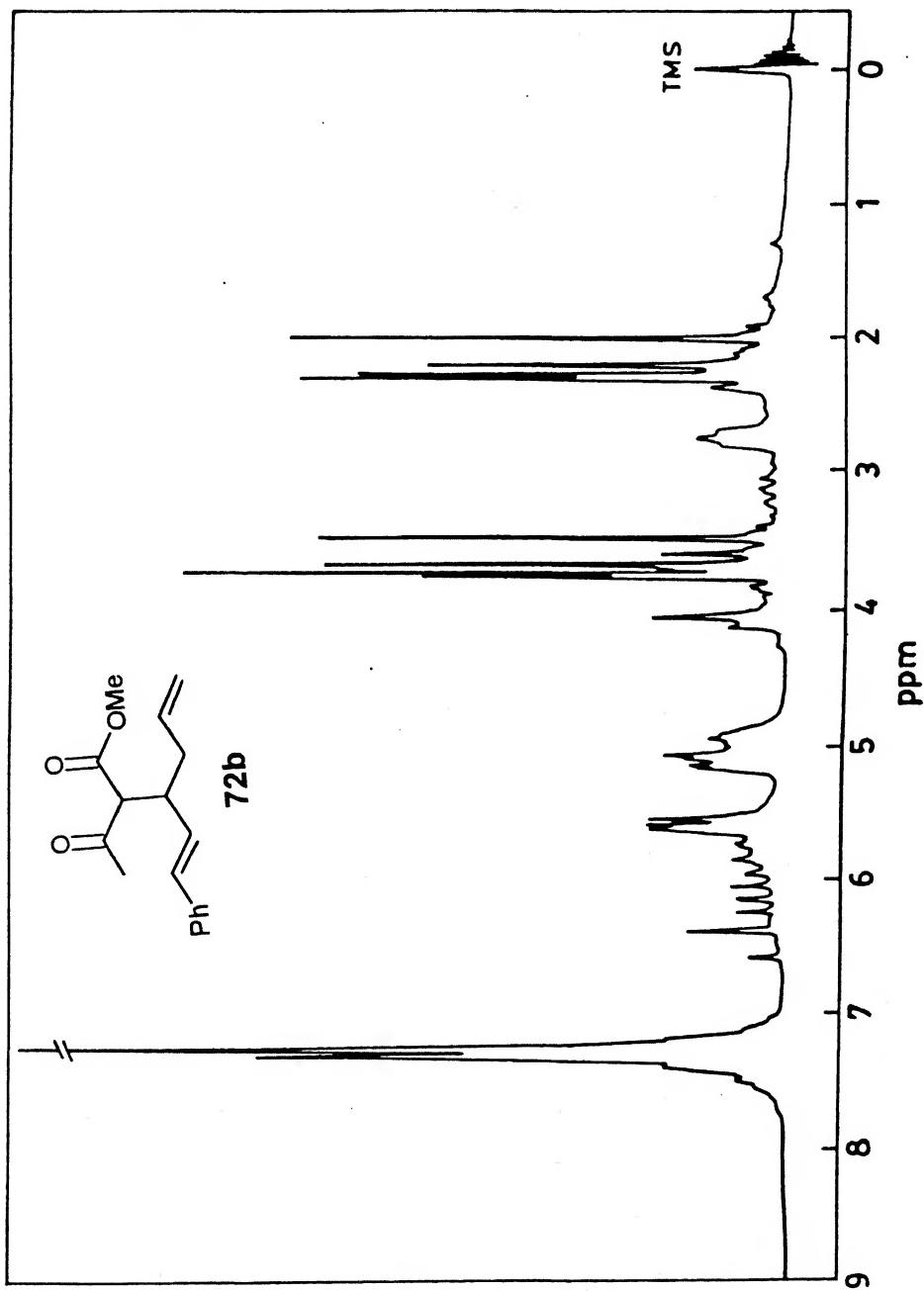
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) :  $\delta$  5.72 (qu, J = 7.5 Hz, 1H), 5.43-5.1 (m, 1H), 4.31-3.78 (m, 3H), 2.7-1.75 (m, 6H), 1.6 (d, J = 7.5 Hz, 3H), 1.5-1.05 (m, 6H), 0.85 (m, 6H).

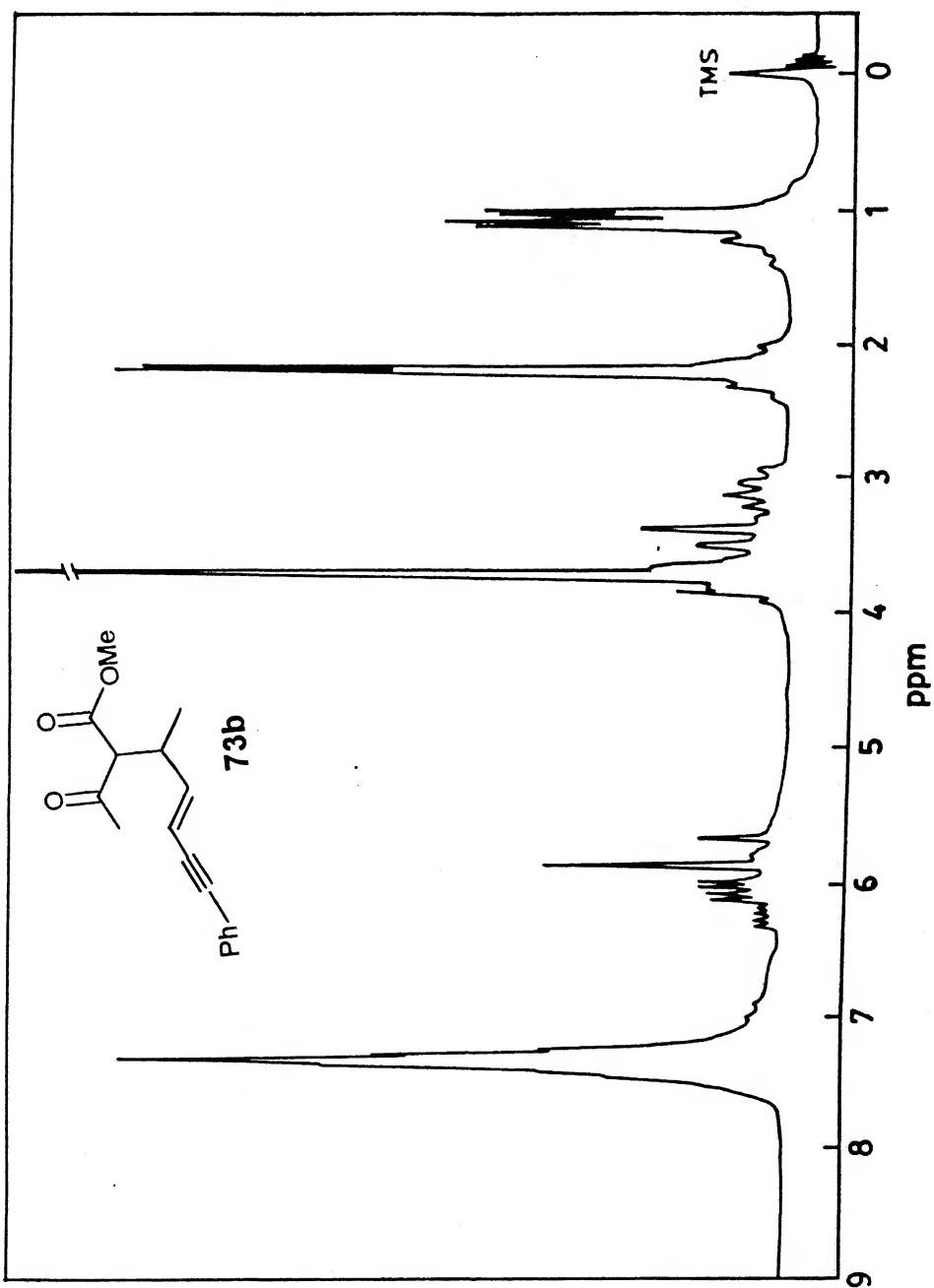
<sup>13</sup>C NMR : 13.46, 13.98, 17.66, 18.29, 19.60, 21.75, 21.85, 29.16, 30.94, 38.63, 39.21, 61.62, 76.73, 77.04, 77.36, 126.04, 129.97, 213.02.

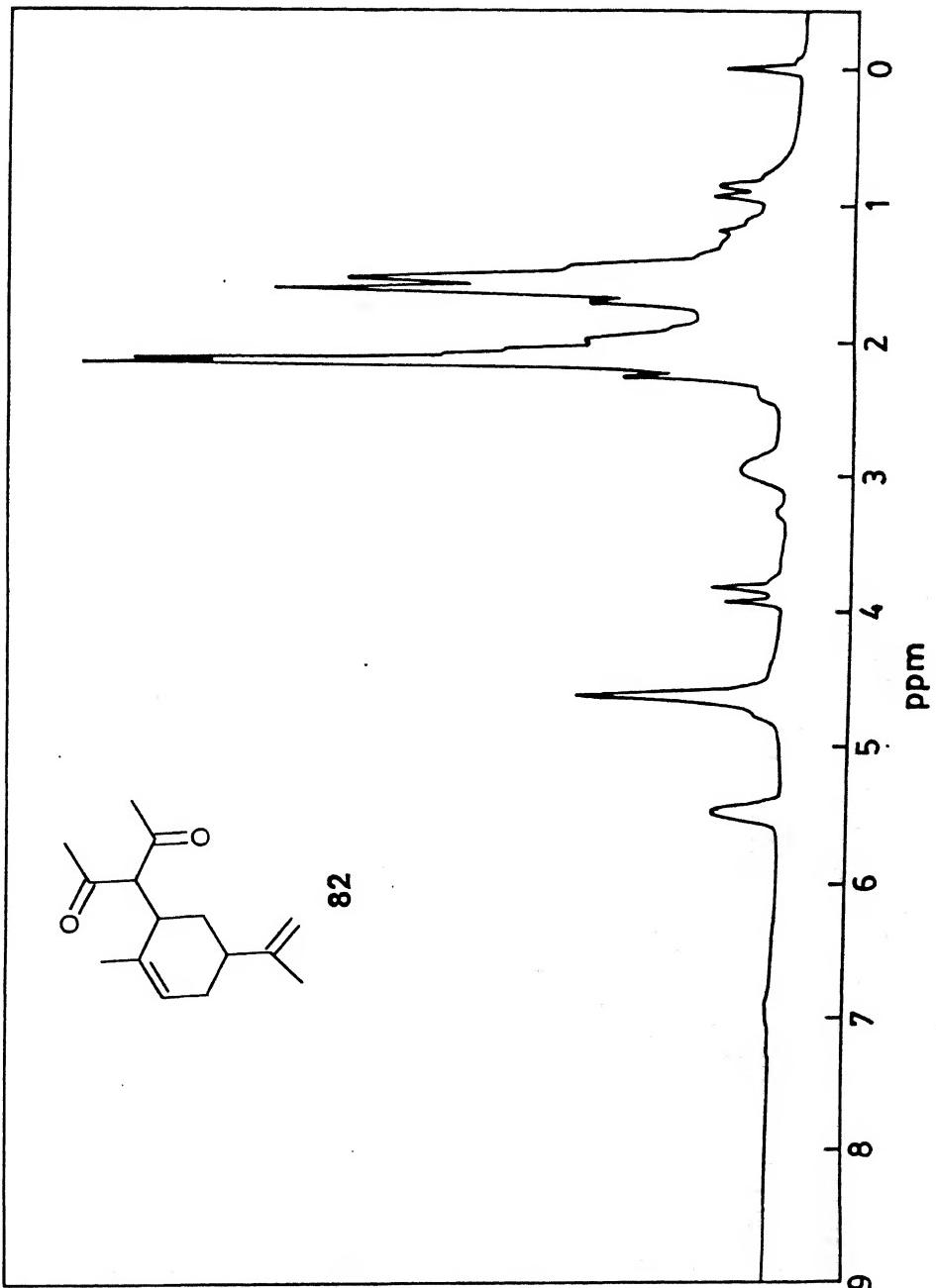
IR (Thin film) :  $\nu_{max}$  2230, 1750, 1720, 1470, 1450, 1230 cm<sup>-1</sup>.

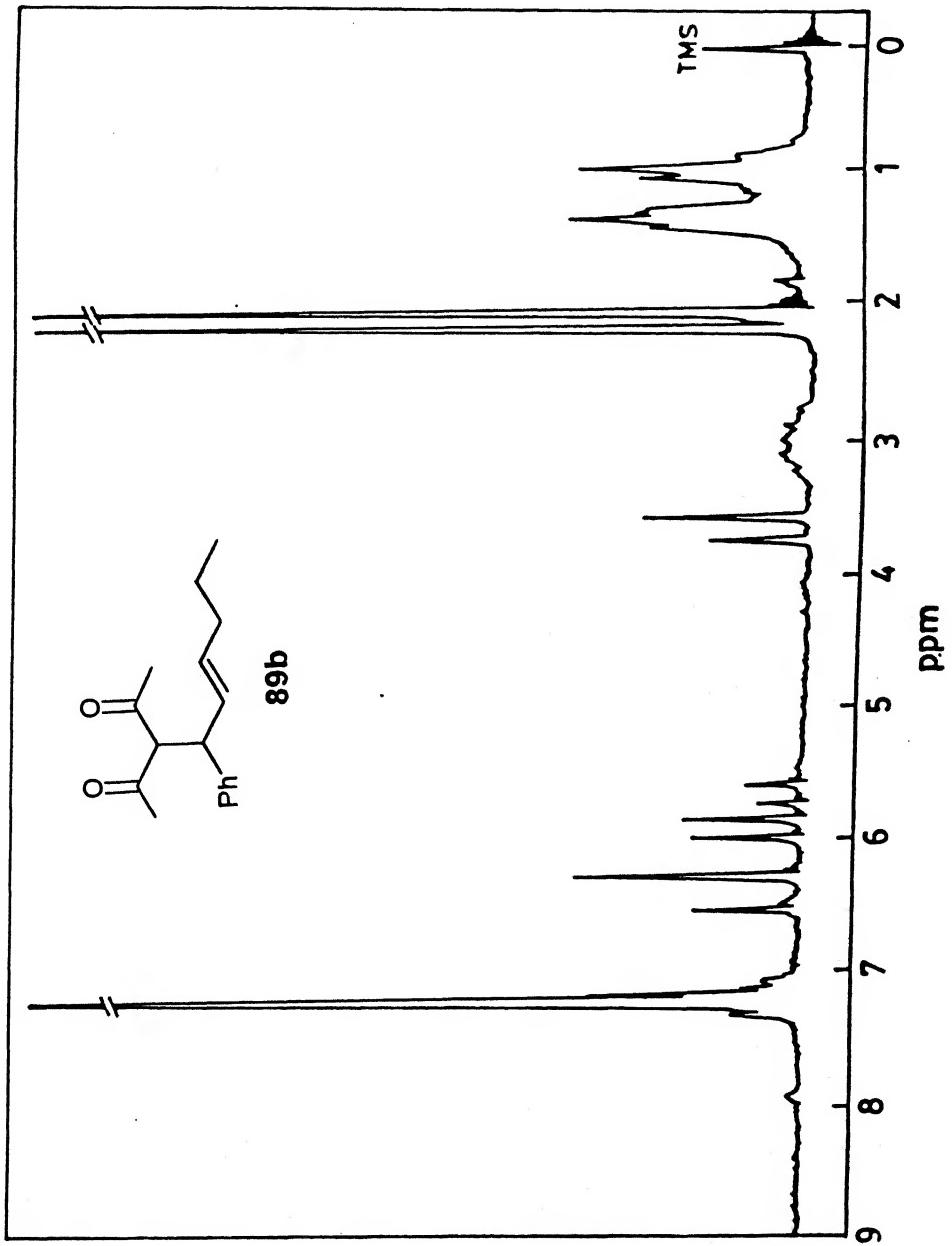
Anal. Calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub> : C, 74.50; H, 8.96

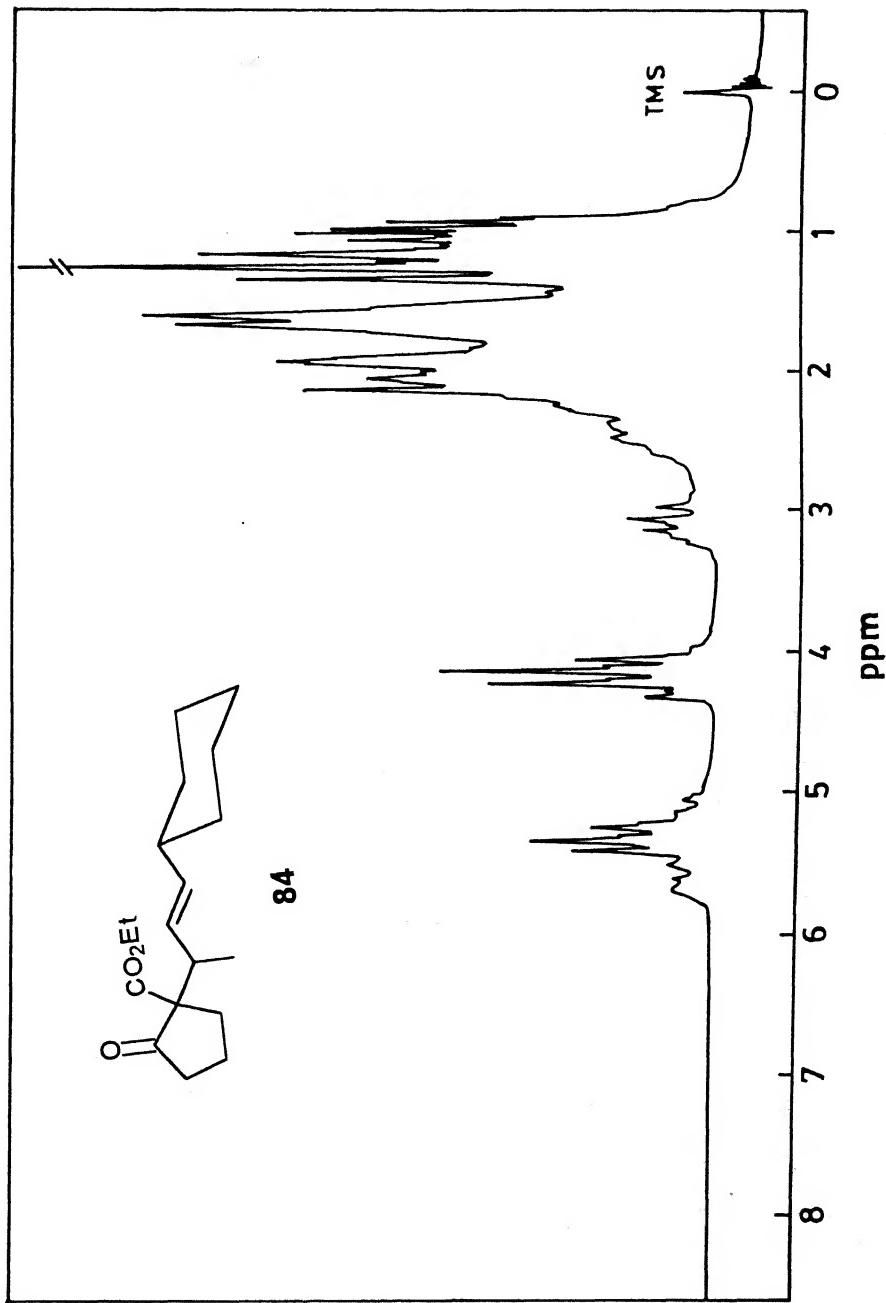
Found : C, 74.59; H, 9.00.

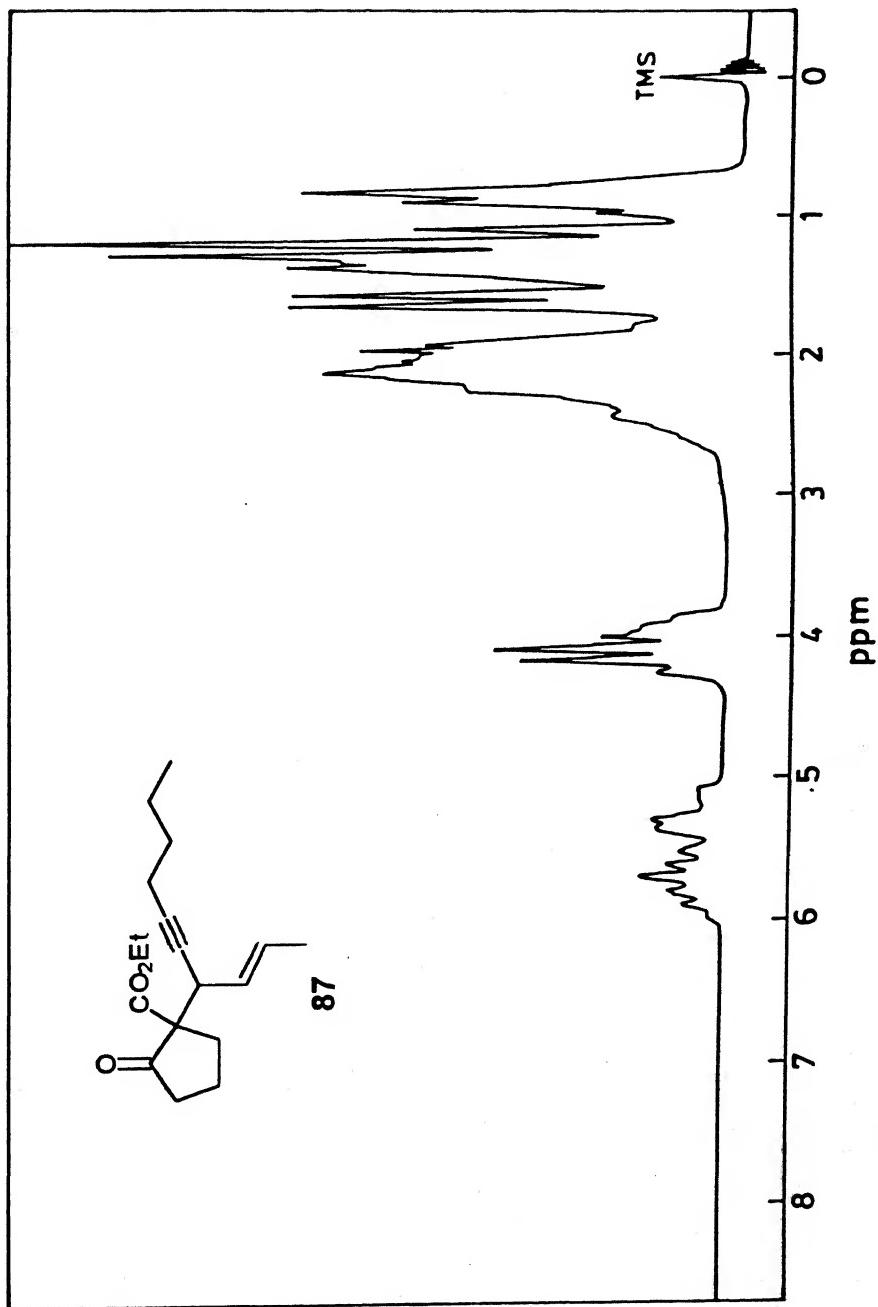


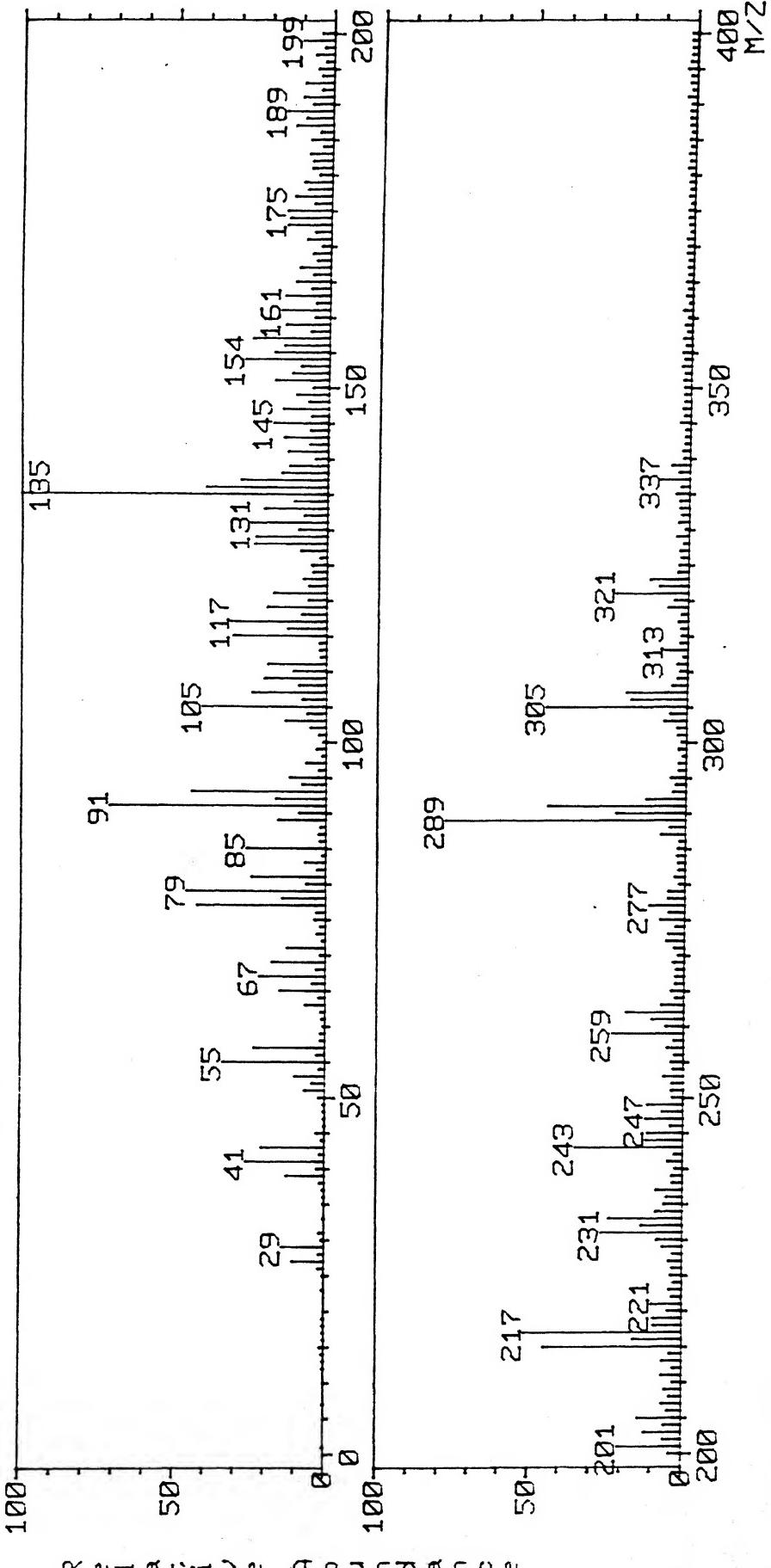
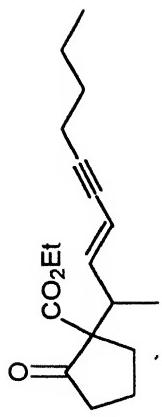












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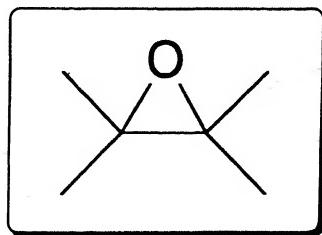
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# **Chapter 4**

## **SECTION - A**

### **COBALT(II) COMPLEX CATALYZED EPOXIDATION WITH MOLECULAR OXYGEN**

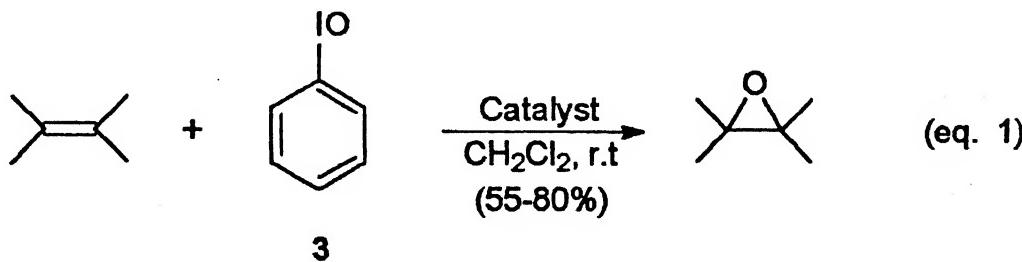
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## 4.1 INTRODUCTION

Epoxide is one of the most useful synthetic intermediates for the preparation of oxygen containing natural products or the production of epoxy resins, etc. Much more effort has been made to develop the direct epoxidation of olefins by use of molecular oxygen. Transition metal complexes catalyzed epoxidation of olefins with molecular oxygen has received considerable attention from organic chemists in the last several years. These oxidations also enjoy paramount importance as mimics for various mono oxygenases catalyzed reactions in the biological systems.

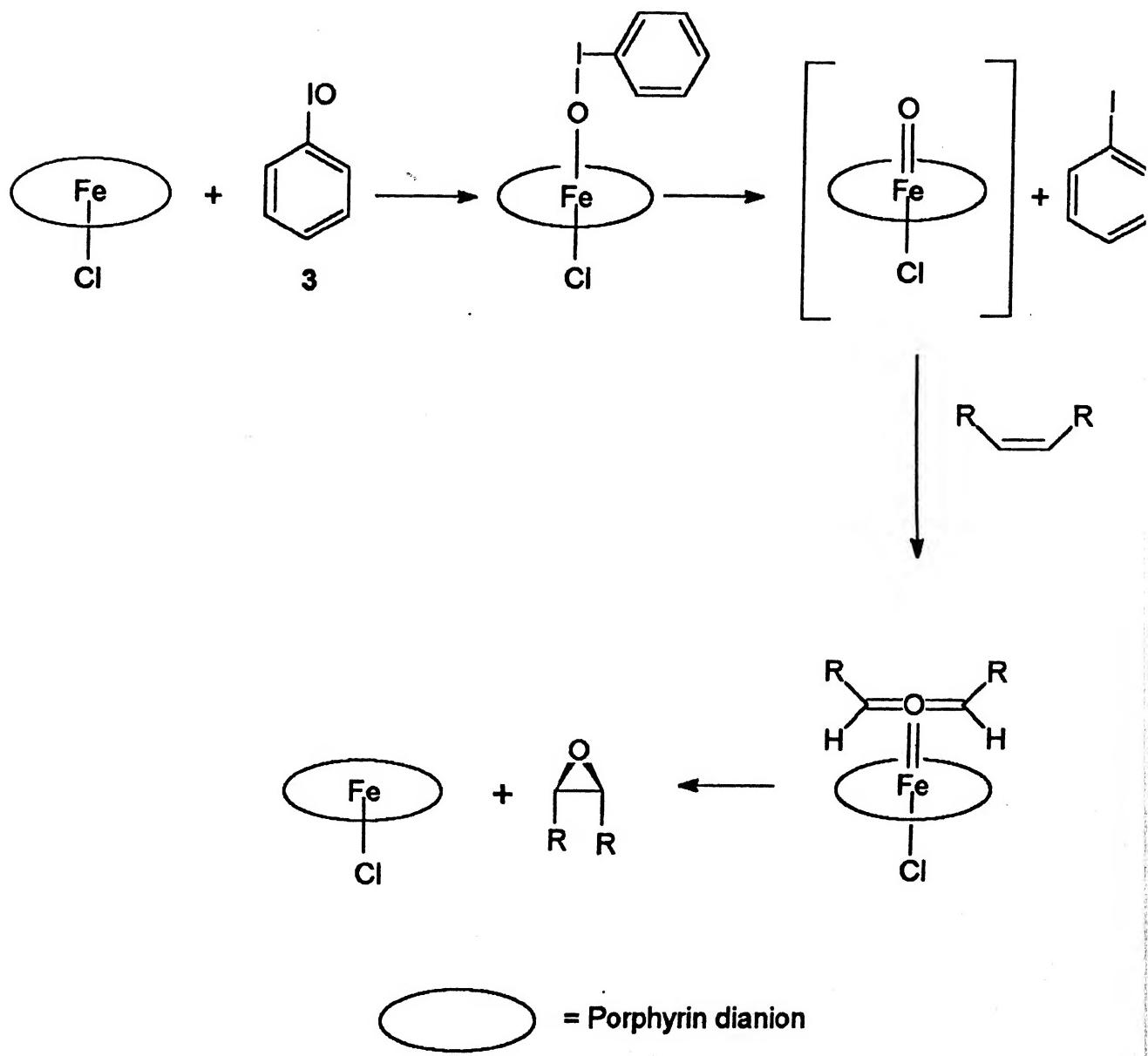
In 1979, Groves and coworkers<sup>1</sup> have found that the iron- porphine complexes, such as chloro- $\alpha, \beta, \gamma, \delta$ -tetra-phenylporphinato iron(III) **1** and chloro dimethyl ferriprotoporphyrin IX **2** catalyze the epoxidation of hydrocarbons with iodosyl benzene **3** as an oxygen source (eq. 1).



The reaction of cis- and trans-stilbene with iodosylbenzene **3** using **2** as a catalyst gave the corresponding cis- and trans- stilbene oxides. Surprisingly, in the presence of catalyst **1**, cis-stilbene was converted to cis-stilbene oxide in 82% yield, but the trans-isomer was inert. Such a change in selectivity with changes in the substitution pattern on the porphyrin suggests that the catalyst is intimately involved in the oxygen transfer step. A mechanism for olefin epoxidation with iron-porphyrin complex<sup>2</sup> is shown in scheme 4.1.

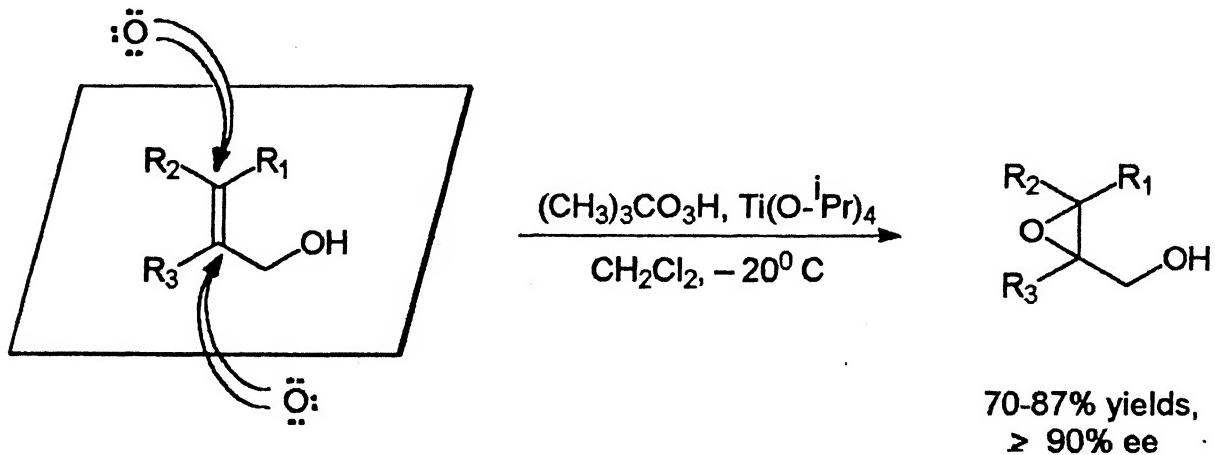
In 1980, Sharpless and Katsuki<sup>3</sup> have discovered a new metal catalyzed asymmetric epoxidation of allylic alcohols using (+)- or (-)-diethyl tartrate titanium tetraisopropoxide, and tert- butylhydroperoxide.

This potential chiral epoxidation system possesses two especially striking features. First, it gives uniformly high asymmetric inductions throughout a range of substitution patterns in the allylic alcohol substrate. Second, upon the use of a given tartrate enantiomer, the system

**Scheme 4.1**

seems obliged to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern (Scheme 4.2). When the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right as shown, the use of L-(+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom, whereas with D-(-)-diethyl tartrate, the epoxide oxygen is added from the top.

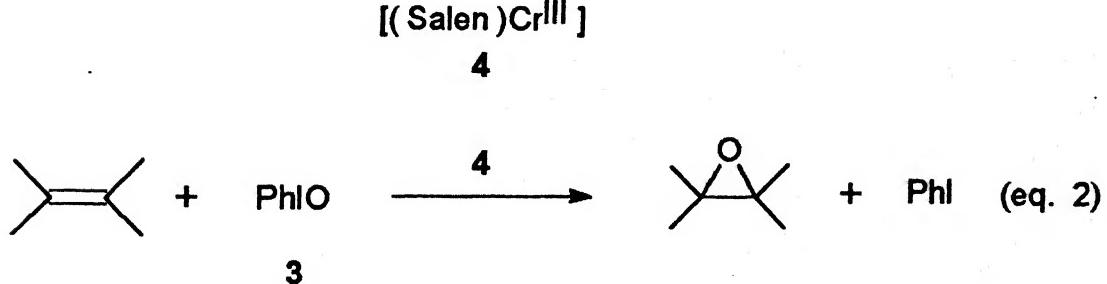
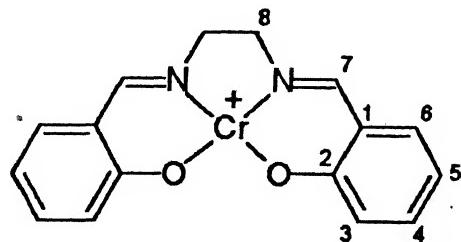
## D-(-)-diethyltartrate (unnatural)



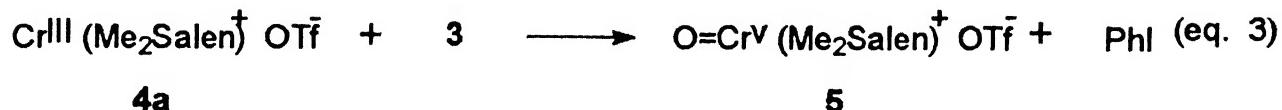
## L-(+)-diethyltartrate (natural)

**Scheme 4.2**

Kochi and coworkers<sup>4</sup>, have prepared a series of chromium cationic salen complexes<sup>5</sup> and used them for the catalytic epoxidation of various olefins with iodosylbenzene **3** in acetonitrile solution (eq. 2). The general structure of the chromium complex **4** is given below.

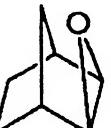
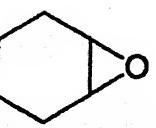


The chromium (III) complexes **4** are readily converted to the corresponding oxochromium (V) species **5** by iodosylbenzene **3** under the reaction conditions of the catalytic process described in eq. 3. These oxochromium (V) species can be isolated as stable compounds.

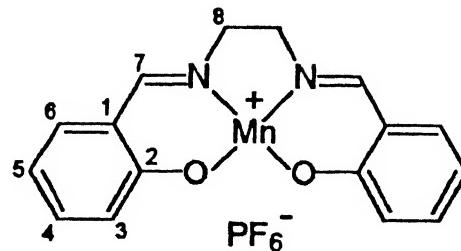


These are prone to the coordination of various types of donor ligands such as pyridine N-oxide. The results of the direct epoxidation of various olefins with oxochromium(V) species **5** with pyridine N-oxide as a cocatalyst are presented in Table 4.1.

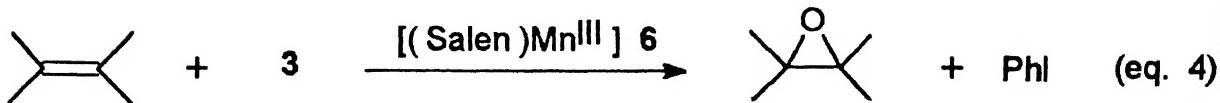
**Table 4.1 : Stoichiometric Epoxidation of Olefins with Oxochromium (v)**

Olefins	Epoxides	Yields(%)
norbornene		100
Styrene		78
Stilbene		47
E		81
Cyclohexene		22

Kochi and coworkers<sup>6</sup> have synthesized manganese(III) salen complexes for the epoxidation of olefins with iodosylbenzene **3** (eq. 4). The general structure of the manganese(III) cationic salen complexes **6** is given below.



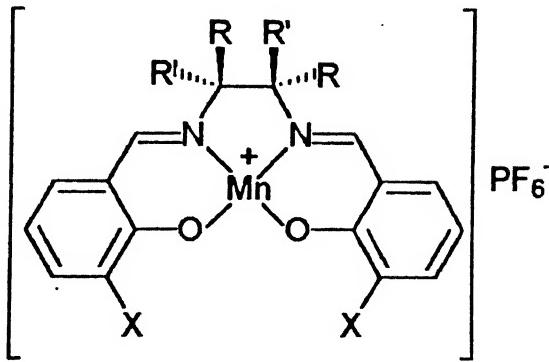
$[(\text{Salen})\text{Mn}^{\text{III}}]$   
**6**



The salen complexes with electron-releasing substituents such as the 5,5'-dimethoxy and 7,7'-diphenyl derivatives effect only poor yields of epoxides, whereas those with 5,5'-dichloro and 5,5'-dinitro substituents lead to the best epoxide yields.

Although, Sharpless and coworkers<sup>3,7</sup> reported highly enantioselective and practical epoxidation of allylic alcohols using a  $\text{Ti}(\text{O-i-Pr})_4$ /diethyl tartrate / tert-butylhydroperoxide system, but enantioselective epoxidation of olefins which do not bear a specific adjacent functionality like a hydroxy group still remains unsettled. Jacobsen and coworkers<sup>8</sup> reported that the manganese complexes of chiral Schiff bases **7** catalyze epoxidation of alkyl and aryl-substituted olefins with high enantioselectivity. The catalysts **7a** and **7c** have been prepared<sup>9</sup> and the reactions were carried out with olefin **8** and iodosylmesitylene **9** as the oxygen atom source (Scheme 4.3). The results are summarized in table 4.2.

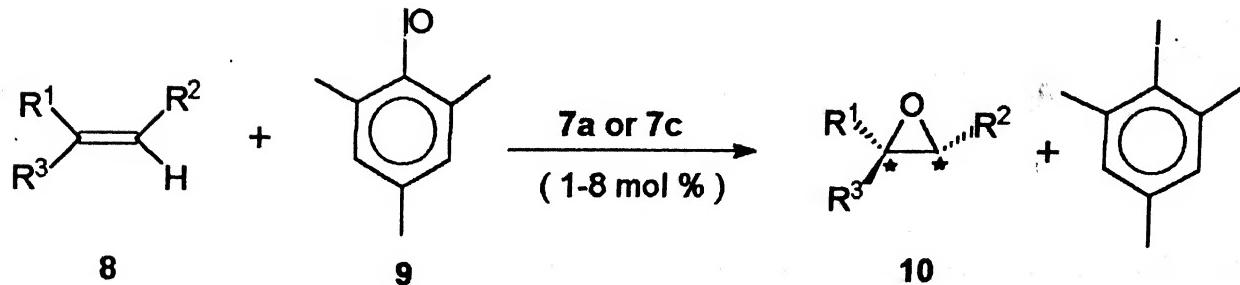
The salen-based catalysts offer important advantages over known chiral porphyrin systems. Their superior enantioslectivity can be attributed to the fact that the complexes bear chirotopic carbons in the vicinity of the metal, resulting in better stereochemical communication in the epoxidation step.



(S, S) - 7a : R = Ph, R' = H, X = H

(R, R) - 7b : R = H, R' = Ph, X = H

(R, R) - 7c : R = H, R' = Ph, X = <sup>t</sup>Bu



Scheme 4.3

**Table 4.2 : Asymmetric Epoxidation of Representative Olefins**

Olefin	Catalyst	Yield %	ee %	Confign.
	(R, R) - 7b	50	59	1R, 2S -(-)
	(S, S) - 7a	63	33	S, S -(-)
	(S, S) - 7a	93	20	1S, 2S -(-)
	(R, R) - 7c	52	93	(-)
	(R, R) - 7c	72	78	1R, 2S -(-)

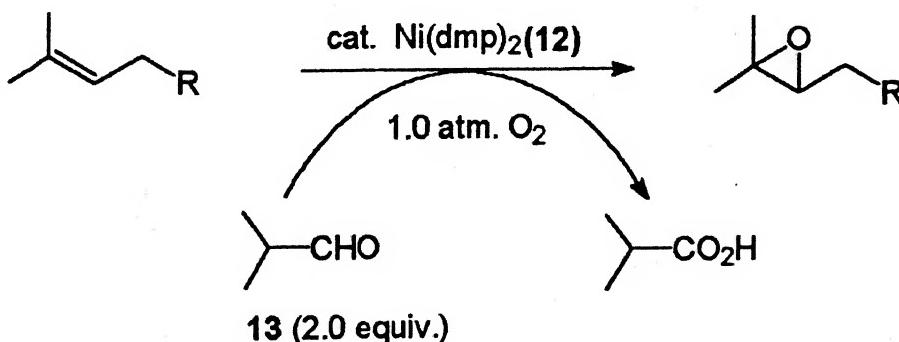
Mukaiyama and coworkers<sup>10</sup> have reported an efficient method for epoxidation of aliphatic or aromatic olefins with molecular oxygen and primary alcohol **11** catalyzed by nickel(II) complexes.

The results of epoxidation of various olefins in the presence of catalytic amount of bis-[1,3-di(p-methoxyphenyl)-1,3-propanedionato] nickel(II) ( $\text{Ni}(\text{dmp})_2$ ) **12** in 1,2-dichloroethane are presented in Table 4.3.

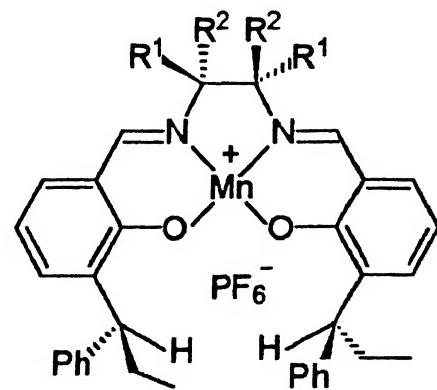
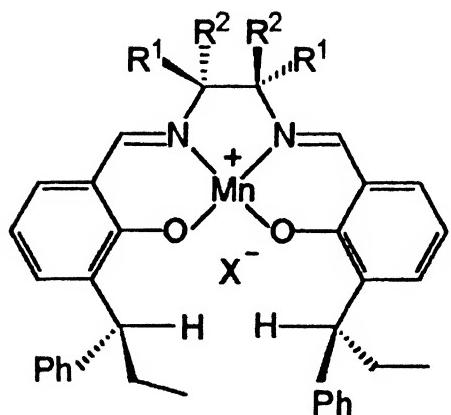
Trisubstituted and exo-terminal olefins or norbornene analogues can be epoxidized<sup>11</sup> in the presence of catalytic amount of nickel(II) complex **12** and aldehyde **13** under an atmospheric pressure of oxygen at room temperature (Scheme 4.4).

**Table 4.3 : Epoxidation of Various Olefins Catalyzed by Ni(dmp)<sub>2</sub>**

Olefin	$\xrightarrow[\text{11}]{\text{O}_2, \text{cat. Ni(dmp)}_2(12)}$	Epoxide	
Entry	Olefin	Alcohol	Epoxide (yield %)
1		n-C <sub>18</sub> H <sub>37</sub> OH	78%
2		n-C <sub>14</sub> H <sub>29</sub> OH	72%
3		n-C <sub>8</sub> H <sub>17</sub> OH	67%
4		n-C <sub>14</sub> H <sub>29</sub> OH	81%

**Scheme 4.4**

Katsuki and coworkers<sup>12</sup> have synthesized the chiral (salen) manganese(III) complexes **14a-c** and used them for catalytic asymmetric epoxidation of unfunctionalized olefins with iodosobenzene **3** as a terminal oxidant.



**14c** :  $R^1 = Ph$ ,  $R^2 = H$

**14a**:  $R^1 = Ph$ ,  $R^2 = H$ ,  $X = OAc$

**14b**:  $R^2 = H$ ,  $R^1 = Ph$ ,  $X = OAc$

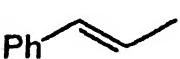
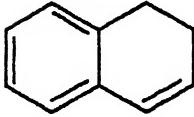
The results of epoxidation of unfunctionalized olefins catalyzed by **14a-c** with **3** in acetonitrile are presented in table 4.4.

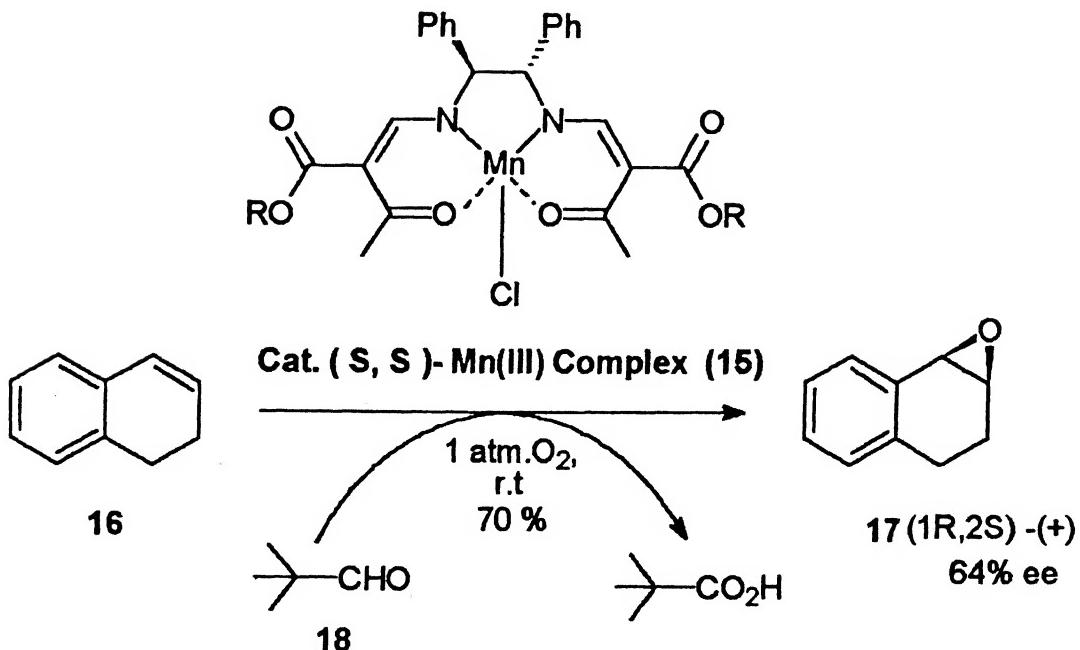
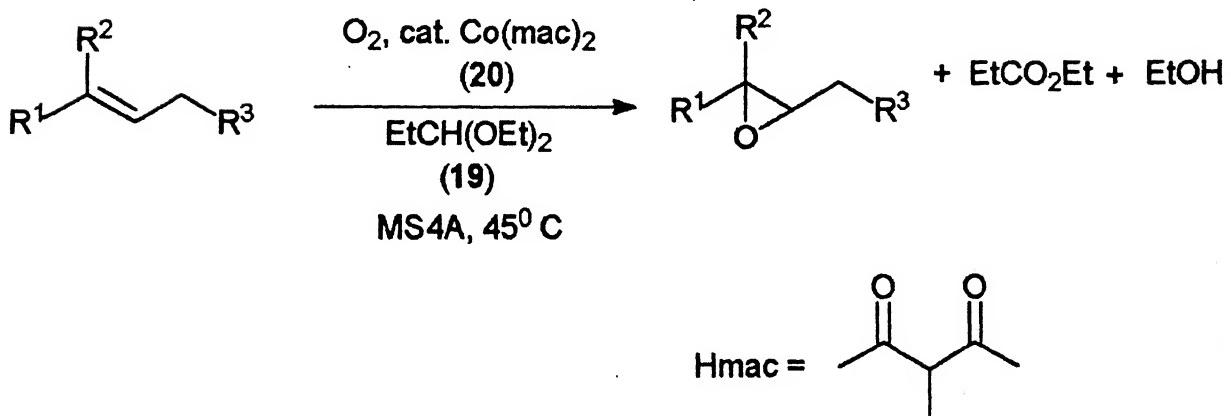
Enantioselectivity was improved by the use of donor ligands such as 2-methyl imidazole, pyridine N-oxide and lutidine N-oxide.

Manganese(III) complex of optically active N,N'-1,2-diphenyl ethylene bis-( $\alpha$ -alkoxycarbonyl- $\beta$ -ketoimine)<sup>13,14</sup> **15** is an effective catalyst for the asymmetric epoxidation<sup>15</sup> of simple olefins **16** to afford the corresponding optically active epoxides **17** with good to high enantioselectivities under an oxygen atmosphere with combined use of an aldehyde **18** (Scheme 4.5).

Mukaiyama and coworkers<sup>16</sup> reported an efficient method for epoxidation of olefins by the combined use of molecular oxygen and propionaldehyde diethyl acetal **19** with cobalt(II) complex catalyst **20** (Scheme 4.6).

**Table 4.4 : Asymmetric Epoxidation of Unfunctionalized Olefins.**

Substrate	Catalyst	Yield %	% ee	Abs. Confign.
	<b>14a</b>	59	3	(1S,2S)
	<b>14b</b>	61	32	(1R,2R)
	<b>14c</b>	32	7	(1R,2R)
	<b>14c</b>	95	48	(1R,2R)
	<b>14b</b>	26	44	(1R,2S)
	<b>14b</b>	93	49	(1R,2S)
	<b>14c</b>	65	72	(1S,2R)

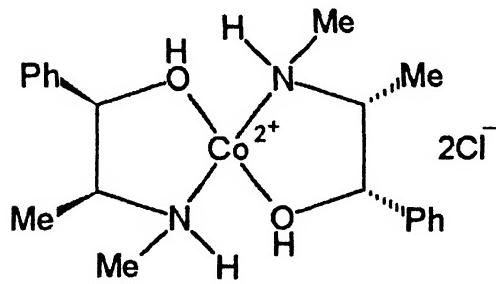
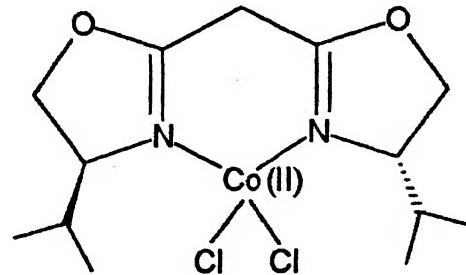
**Scheme 4.5****Scheme 4.6**

## 4.2 PRESENT STUDY

It is clear from foregoing section that epoxides are versatile organic intermediates in a wide range of synthetic transformations. Thus the synthesis and reactions of epoxides provide an exciting area of research. Enantioselective synthesis of epoxides is enjoying increasing importance in the domain of modern organic synthesis. Realization of this goal under the aegis of a chiral catalyst seems an exciting possibility and as a result to this hectic research activity is witnessed from the recent literature.

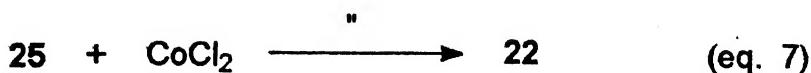
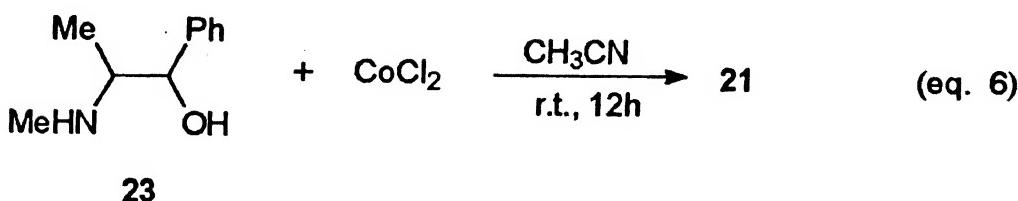
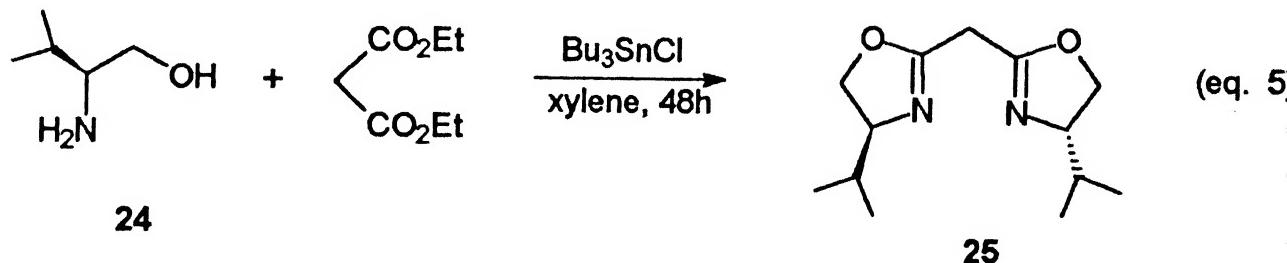
Transition metal catalyzed epoxidation of olefins with molecular oxygen has received considerable attention from organic chemist in the last several years. These oxidations also enjoy paramount importance as mimics for various monooxygenases catalyzed reactions in the biological systems.

In order to achieve enantioselective epoxidation, we have prepared cobalt complexes **21** and **22** with ligands derived from L-ephedrine **23** and S-valinol **24**. The synthesis of complex

**21****22**

**22** was carried out by using ligand<sup>17</sup> **25** which can be derived from the reaction of S-valinol **24**, diethyl malonate and catalytic amount of tributyl tin chloride (eq. 5).

Thus the catalyst **21** and **22** can be achieved by treating  $\text{CoCl}_2$  with **23** or **25** in acetonitrile at room temperature (eq. 6,7).



These catalysts were characterised by UV-visible IR, magnetic susceptibility measurements and combustion analysis. The geometry in both the cases were found to be tetrahedral and the conductivity measurements indicate that the catalyst **21** is ionic in nature. These catalysts are crystalline green coloured solids and are thermally stable at room temperature under atmospheric oxygen. Cobalt complex **21** is insoluble in 1,2-dichloroethane and the reaction with this is likely to be catalyzed under heterogenous conditions. Cobalt complex **22** is soluble in acetonitrile and thus it catalyzes the reaction as homogenous catalyst.

We have used these catalysts in conjunction with 2-methyl propanal which acts as a reductant during these reactions.

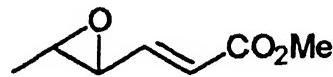
Thus the reaction of various olefins with molecular oxygen and 2-methyl propanal in the presence of catalyst **21** or **22** give the corresponding epoxides in good yields. The results of these epoxidations are compiled in table 4.5. Trans-stilbene **26a** can be smoothly converted to the corresponding epoxide **27a** in high yield. This epoxidation is quite facile for di- and tri-substituted olefins **26b** and **26c** as seen from the reaction of various dienes in the presence of catalyst **21** or **22** (table 4.5, entries 3 and 5). Interestingly, the triene **26e** underwent smooth

Table 4.5 : Epoxidation of olefins using catalyst 21 and 22.

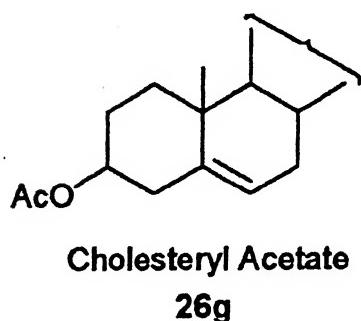
Entry	Olefins	Catalyst	Product(yield%)
1		21	
2		22	
3		21	
4		22	
5		21	
6		22	
7		22	
8		21	
9		22	

Table 4.5 continued.....

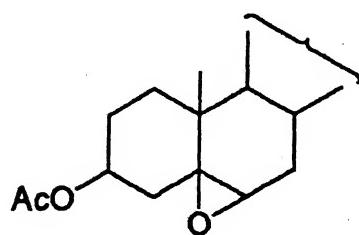
10



21



21



11

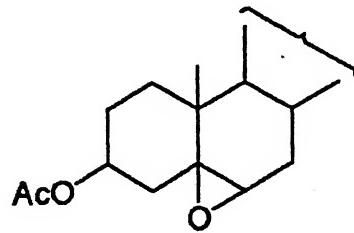
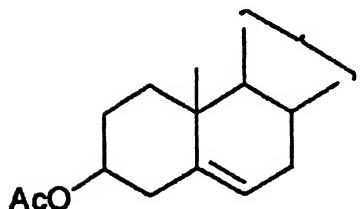
21

27g(87)

12

22

27g(87)



13

21

27h(48)  
 $\alpha : \beta = 76 : 24$

14

22

27h(58)

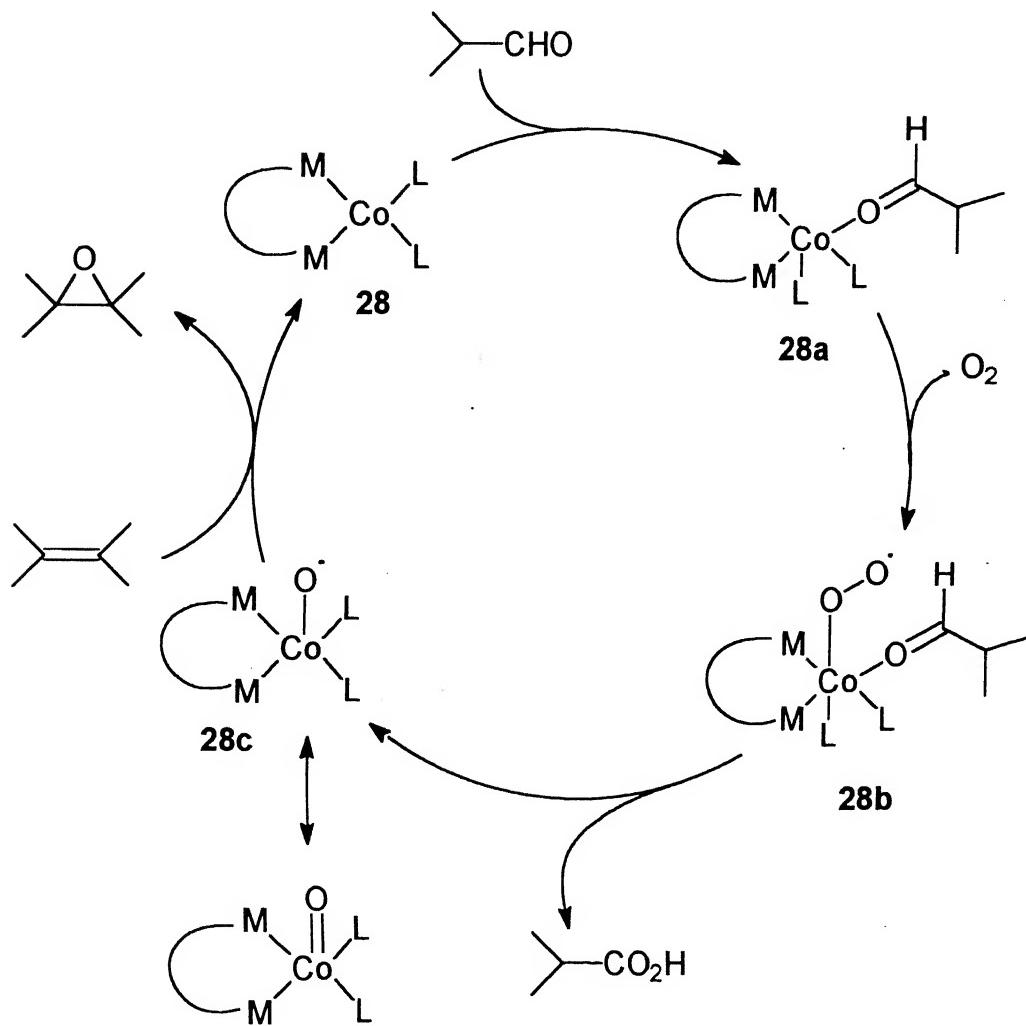
monoepoxidation at the trisubstituted unfunctionalized double bond (Table 4.5, entry 8) in the presence of catalyst **21** or **22**. The epoxidation of the dienes and triene did not give any other mono or diepoxides under these conditions. Based on the epoxidation of these olefins, it can be seen that the order of reactivity of various double bonds under these conditions is : trisubstituted > allylic  $\gg$  terminal (monosubstituted). The conjugated diene like methyl sorbate **26f** gave a moderate yield of the monoepoxide **27f** (Table 4.5, entry 10) in the presence of catalyst **22**. Similarly, the oxygenation of the acetates of cholesterol **26g** and diosgenin **26h** gave the corresponding epoxides **27g** and **27h** respectively as a mixture of diastereomers in high yields (Table 4.5, entries 11 and 13).

Studies using catalyst **21** and **22** revealed that the epoxidation occurs in very high chemical yields, however, no enantioselectivity was observed during the epoxidation using these catalysts. Changing the reaction conditions like solvent and temperature did not bring about any enantioselectivity using catalyst **21** or **22**.

The role of 2-propanal is quite important in these reactions as the other aldehydes like propanal or butanal do not bring about this transformation in good chemical yields. Recently, a similar observation was made by Mukaiyama and coworkers<sup>10,11,13</sup> during the epoxidation of alkenes with molecular oxygen.

A careful analysis of reaction mixture has indicated that the 2-methyl propanal undergoes oxidation to the corresponding carboxylic acid. This observation indicates that the aldehyde is mainly acting as a reducing agent. These reactions are not likely to proceed via a peracid derived from 2-methyl propanal. As it is known that allylic acetates undergo epoxidation under these conditions. But the results from the epoxidation of **26b**, **26c** and **26e** clearly indicate that the latter are not derived by peracid oxidations. Thus inability of allylic double bond of allylic acetate to undergo epoxidation supports that the epoxidizing species is not a peracid. In view of these observations, we feel that these epoxidations are proceeding via *in situ* generated cobalt oxo complexes (Scheme 4.7).

The initial coordination of 2-methyl propanal is likely to enhance the interaction of oxygen.

**Scheme 4.7**

It has already been shown that 2-methyl propanal brings about remarkable dioxygen coordinating ability to nickel<sup>11</sup> and cobalt<sup>16</sup> complexes. Thus it is conceivable that the oxygen and aldehyde adduct **28b** may provide the carboxylic acid and cobalt oxo complex **28c**. Such complexes of iron have already been speculated to be oxygen transfer species in studies using iron porphyrin complex<sup>2,4</sup>.

In conclusion, the present route for epoxidation has an advantage over the method of Mukaiyama and Katsuki as a) it can be performed at ambient temperature and at normal pressure of oxygen and b) the dienes can be converted to monoepoxide exclusively. Unfortu-

nately no enantioselectivity was observed using either of these catalysts. These studies have shown that high chemical yield of epoxides can be achieved under these conditions. Future efforts will be directed towards achieving the enantioselectivity by modifying the ligands and experimental conditions.

## 4.3 EXPERIMENTAL

### Materials and Methods

Acetonitrile, 1,2-dichloroethane, N,N-dimethyl formamide, diethyl ether, acetic anhydride, triethylamine were purified by the standard procedure. Cobalt(II) chloride was purchased from LOBA India, Ltd. Bombay and dried at  $\sim 120^\circ \text{C}$  for 2-3 h prior to use. Column chromatography was performed by using ACME silicagel (60-120 mesh). Aldehydes, olefins and chiral amines were purchased commercially. Olifinic acetates were prepared by standard procedures.  $^1\text{H-NMR}$  spectra were recorded at 60 and 80 MHz in  $\text{CDCl}_3$  or  $\text{CCl}_4$ . IR spectra were recorded on a Perkin Elmer 683 Spectrometer. Elemental analysis was conducted using Coleman automatic C, H and N analyzer. All the known compounds were characterized by comparing the data from the literature.

### Synthesis of Chiral Cobalt Complexes

Chiral ligand (10 mmol) was taken in dry acetonitrile (20 mL) and  $\text{CoCl}_2$  (5 mmol) was added rapidly under nitrogen atmosphere and stirred for 12 hours. The solvent was evaporated in vacuo. The residue was crystallized from dry diethyl ether.

Chiral cobalt complex derived from L-ephedrine **21**.

UV (DMSO) :  $\lambda_{max}$  679, 623 and 614 nm

IR (KBr) :  $\nu_{max}$  3540, 3320  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{30}\text{N}_2\text{Cl}_2\text{Co}$ : C, 56.10; H, 7.00

Found : C, 56.37; H, 7.19.

Catalyst **22** was prepared from L-valinol [(S)-(+)-2-amino 3-methyl-1 butanol] as described in ref. 17.

Magnetic susceptibility measurement by NMR method (EVAN's method) of the complex.

$$x_V = \frac{3 \times \Delta f}{2\pi fm} + x_o$$

$\Delta f$  = shift in TMS peak

$f$  = instrument frequency ( $60 \times 10^6$  Hz)

$m$  = weight of the compound (in grams) in 1 ml.

$x_v$  = volume susceptibility of solvent

$x_M = x_v \times$  molecular weight of the complex

$$\mu_{\text{eff}} = 2.83 \sqrt{x_m \times T}$$

$$T = 435.5 - 1.193(\Delta f') - 29.3(\Delta f' \times 10^{-2})^2$$

$\Delta f'$  is measured from methanol spectrum shift between two peaks.

$$\text{Now, } x_v(DMSO) = -0.602 \times 10^{-6}.$$

In the NMR spectra, 300 div. = 120 Hz

$$50 \text{ div.} = 20 \text{ Hz} = \Delta f.$$

Shift between two peaks = 50 divisions.

$$\text{Hence, } x_v = \frac{3 \times 20}{2 \times 3.14 \times 60 \times 10^6 \times 0.008} - 0.602 \times 10^{-6}$$

5 ml of soln. contains 40 mg complex.

Hence,  $m = 0.008 \text{ gm}$

$$\text{Therefore, } x_v = 19.30246 \times 10^{-6}$$

Molecular weight of the catalyst is 460.48

$$\text{Hence, } x_M = x_v \times 460.48$$

$$= 0.00889$$

Therefore,

$$\mu_{\text{eff}} = 2.83 \sqrt{0.00889 \times 307.8}$$

where.  $307.8 = T$

Hence,  $\mu_{eff} = 4.69$

Literature value for Co(II) tetrahedral complex

$$\mu_{eff} = 4.7.$$

### Preparation of Allylic Acetates

Allylic acetates were prepared as described in Chapter 3.

#### Geranyl acetate 26b

$^1H$ -NMR ( $CDCl_3$ ) :  $\delta$  5.3-4.9 (m, 2H), 4.4 (d,  $J = 7.0$  Hz, 2H), 2.0 (m, 7H), 1.6 (d,  $J = 6.0$  Hz, 9H).

#### Linalyl acetate 26c

$^1H$ -NMR ( $CDCl_3$ ) :  $\delta$  6.1-5.5 (m, 1H), 5.0 (m, 3H), 2.0 (s, 3H), 1.9 (m, 4H), 1.6 (s, 3H), 1.55 (s, 3H), 1.5 (s, 3H).

#### 3-Acetoxy-5,9-dimethyl, deca 1,4,8-triene 26e

$^1H$ -NMR ( $CCl_4$ ) :  $\delta$  5.9-5.25 (m, 3H), 5.2-4.7 (m, 5H), 2.0 (m, 4H), 1.9 (s, 3H), 1.6 (s, 3H) 1.55 (s, 3H), 1.5 (s, 2H).

### General Procedure for the Synthesis of Epoxide from Unactivated Olefins

To a solution of olefin (10 mmol) in 1,2-dichloroethane were added catalyst **21** (5 mol %) and 2-methyl propanal (20 mmol) and the resulting mixture was stirred under an oxygen atmosphere (by putting an oxygen balloon) for 12-15 hrs. at ambient temperature. Removal of the solvent gave a residue which was taken into dichloromethane (50 mL) washed with saturated solution of sodium bicarbonate and water. Drying ( $MgSO_4$ ) and removal of solvent

yielded a residue which on column chromatography ( $\text{SiO}_2$ ) afforded the epoxide. These reactions were also performed with catalyst **22** as described above. However, dry acetonitrile instead of 1,2-dichloroethane was used as a solvent in this case.

### Trans- stilbene oxide **27a**

Trans- stilbene **26a** (1.80g, 10 mmol) and isobutyraldehyde (1.44g, 20 mmol) were subjected to the reaction conditions as described above. Column chromatography afforded **27a** (1.76 g, 90%) as a solid, m.p. 67-69° C.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.3 (s, 10H), 3.7 (s, 2H).

IR (KBr) :  $\nu_{max}$  3060, 1370, 1245  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{O}$  : C, 85.72; H, 6.12.

Found: C, 85.85; H, 6.15.

### 1-Acetoxy 3,7-dimethyl 6,7-epoxy oct-2-ene **27b**

This compound was prepared from geranyl acetate **26b** (0.98g, 5 mmol) and isobutyraldehyde (0.72g, 10 mmol) in 1,2-dichloroethane (30 mL) in the presence of catalyst **21** (10 mg) in 60% (0.63g) yield as a yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  5.4 (t,  $J = 7.5$  Hz, 1H), 4.6 (d,  $J = 7.5$  Hz, 2H), 2.75 (t,  $J = 6.25$  Hz, 1H), 2.4-2.10 (m, 2H), 2.05 (s, 3H), 1.9-1.56 (m, 5H), 1.3 (d,  $J = 3.75$  Hz, 6H,  $-(\text{CH}_3)_2$ ).

IR (Thinfilm) :  $\nu_{max}$  3040, 1730, 1660, 1370, 1230  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}_3$  : C, 67.94; H, 9.43.

Found: C, 68.01; H, 9.45.

### 3-Acetoxy 3,7-dimethyl 6,7-epoxy oct-1-ene **27c**

Linalyl acetate **26c** (0.98g, 5 mmol), isobutyraldehyde (0.72g, 10 mmol) and catalyst **21** in 1,2-dichloroethane were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **27c** (0.89g, 84%) as a colourless liquid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  6.22-5.78 (dq,  $J = 18.75$  and 3.75 Hz, 1H), 5.3-5.05 (m, 2H), 2.75 (t,  $J = 6.25$  Hz, 1H), 2.05 (s, 3H), 2.0-1.85 (m, 2H), 1.75-1.57 (m, 5H), 1.3 (d,  $J = 3.75$  Hz, 6H,  $-(\text{CH}_3)_2$ ).

IR (Thinfilm) :  $\nu_{max}$  3100, 1730, 1640, 1370, 1240  $\text{cm}^{-1}$ .

Anal. Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>3</sub> : C, 67.94; H, 9.43.

Found: C, 68.06, H, 9.47.

#### **4-Acetoxy 5,6-epoxy 6-phenyl hex-1-ene 27d**

Allyl acetate **26d** (1.08g, 5 mmol) and isobutyraldehyde (0.72g, 10 mmol) and catalyst **22** (10 mg) in dry acetonitrile (30 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **27d** (0.64g, 55%) as a colourless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.1 (s, 5H), 6.0-4.5 (m, 4H), 3.55 (d, J = 2.0 Hz, 1H), 2.9 (dd, J = 6.0 and 2.0 Hz, 1H), 2.4 (t, J = 6.0 Hz, 2H), 2.0 (s, 3H).

IR (Neat) : ν<sub>max</sub> 3070, 1725, 1630, 1360, 1230 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>O<sub>3</sub> : C, 72.43; H, 6.89.

Found : C, 72.58; H, 6.94.

#### **4-Acetoxy 6,10-dimethyl 9, 10-epoxy undec-1,5-diene 27e**

The reaction was performed with allyl acetate **26e** (0.94g, 4 mmol) and isobutyraldehyde (0.58g, 8 mmol) in 1,2-dichloroethane in the presence of catalyst **21** (10 mg) to afford **27e** (0.25g, 25%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 6.0-5.4 (m, 2H), 5.28-4.95 (m, 3H), 2.72 (t, J = 6.25 Hz, 1H), 2.3 (m, 4H), 2.05 (s, 3H), 1.87-1.56 (m, 5H), 1.34 (s, 6H).

IR (Neat) : ν<sub>max</sub> 3050, 1730, 1370, 1230 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub> : C, 71.44; H, 9.52.

Found : C, 71.56; H, 9.59.

#### **Methyl 4,5-epoxy hex-2-enoate 27f**

This compound was prepared by the reaction of methyl sorbate **26f** (1.26g, 10 mmol) and isobutyraldehyde (1.44g, 20 mmol) in the presence of catalytic amount of catalyst **22** (10 mg) in dry acetonitrile (30 mL) in 13% (0.18g) yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.0-5.7 (m, 2H), 4.6 (s, 3H), 3.6 (s, 3H), 1.1 (d, J = 6.5 Hz, 3H).

IR (Thinfilm) : ν<sub>max</sub> 3090, 1720, 1650, 1260 cm<sup>-1</sup>.

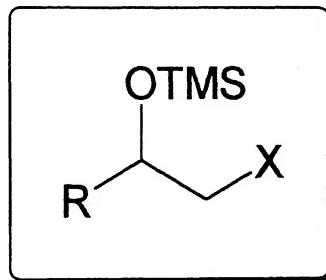
Anal. Calcd. for C<sub>7</sub>H<sub>10</sub>O<sub>3</sub> : C, 59.17; H, 7.04.

# Chapter 4

## SECTION - B

### COBALT(II) CHLORIDE CATALYZED CLEAVAGE OF OXIRANES WITH HETEROATOM NUCLEOPHILES

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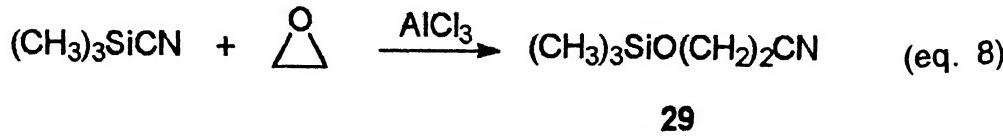


## 4.4 INTRODUCTION

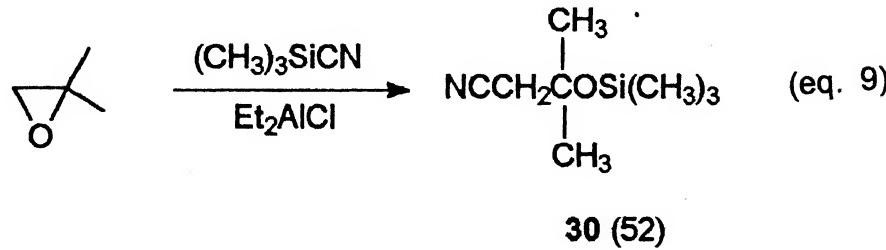
$\beta$ -Amino alcohols are widely occurring in nature and often constitute a critical moiety in the structure of biologically active natural products. These  $\beta$ -amino alcohols can be synthesized by opening of epoxides with nitrogen containing nucleophiles, such as trimethylsilyl cyanide and trimethylsilyl azide.

Trimethylsilyl cyanide is well known to exist in equilibrium with its isocyanide<sup>18</sup> and due to this ambident nature, one may, by judicious choice of an appropriate catalyst, selectively obtain either  $\beta$ - [(trimethylsilyl)oxy] nitriles or isonitriles.

It has been reported<sup>19</sup> that the epoxides react with trimethylsilyl cyanide in the presence of aluminium chloride to yield 3-[(trimethylsilyl)oxy] propionitrile **29** (eq. 8).

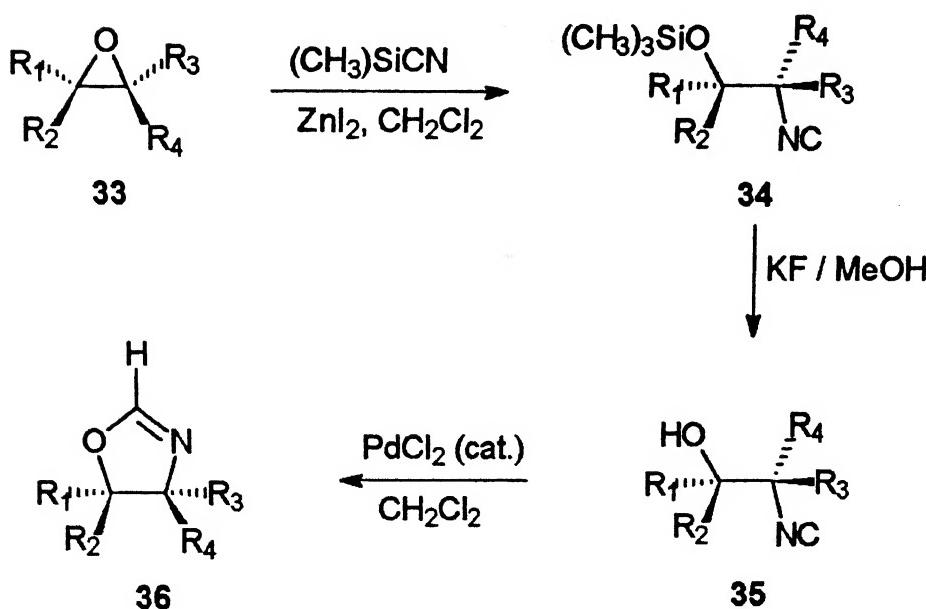
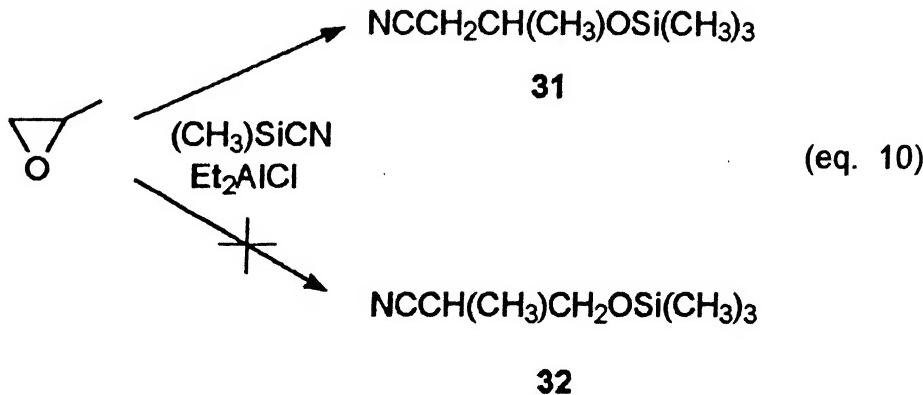


The reaction<sup>20</sup> of trimethylsilyl cyanide with isobutylene oxide with both aluminium chloride and diethyl aluminium chloride afforded 3-methyl-3-[(trimethylsilyl)oxy] butyronitrile **30** (eq. 9), whereas, propylene oxide afforded the 3-methyl 3-[(trimethylsilyl)oxy] propionitrile



**31** rather than 2-methyl-2-[(trimethylsilyl)oxy] propionitrile **32** in the presence of diethyl aluminium chloride (eq. 10).

Gassman and coworkers<sup>21</sup> have reported that the trimethylsilyl cyanide reacts with epoxides **33** in the presence of zinc iodide to produce the trimethylsilyl ether of  $\beta$ -hydroxy isonitriles **34**. These  $\beta$ -hydroxy isonitriles can be converted to the substituted oxazolines **36** (Scheme 4.8).

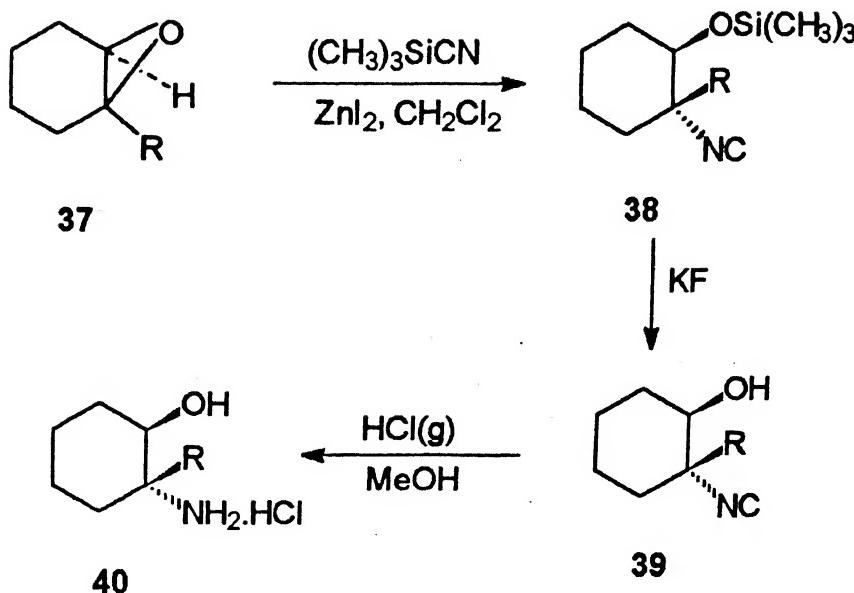
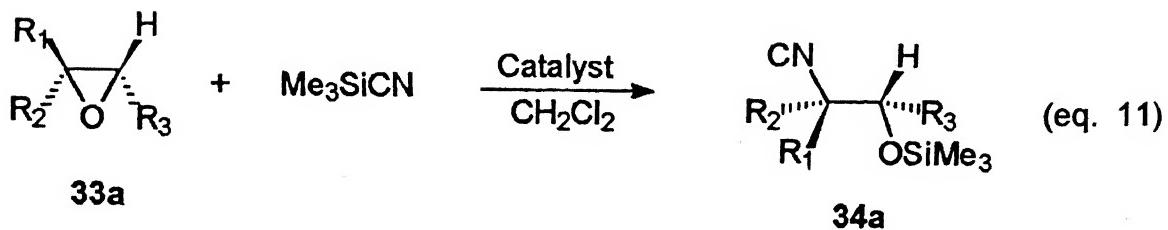


**Scheme 4.8**

$\beta$ -Amino alcohols also can be synthesized by the hydrolysis of these isonitriles. For instance, 2-aminocyclohexanol **40** can be prepared from the cyclohexene oxide **37** as shown in the scheme 4.9.

Trimethylsilyl cyanide reacts<sup>22</sup> with oxiranes **33a** under the catalytic action of Lewis acids such as  $\text{Pd}(\text{CN})_2$ ,  $\text{SnCl}_2$  and  $\text{Me}_3\text{Ga}$ <sup>23</sup> to afford 2-trimethylsilyloxy isocyanides **34a**. These Lewis acid catalyzed reactions proceed under milder conditions to give isonitriles in good yields (eq. 11).

Regio- and stereoselective isocyanosilylation with trimethylsilyl cyanide can be explained:  
 (1) coordination of Lewis acids to oxygen activate oxiranes by stretching the bond between

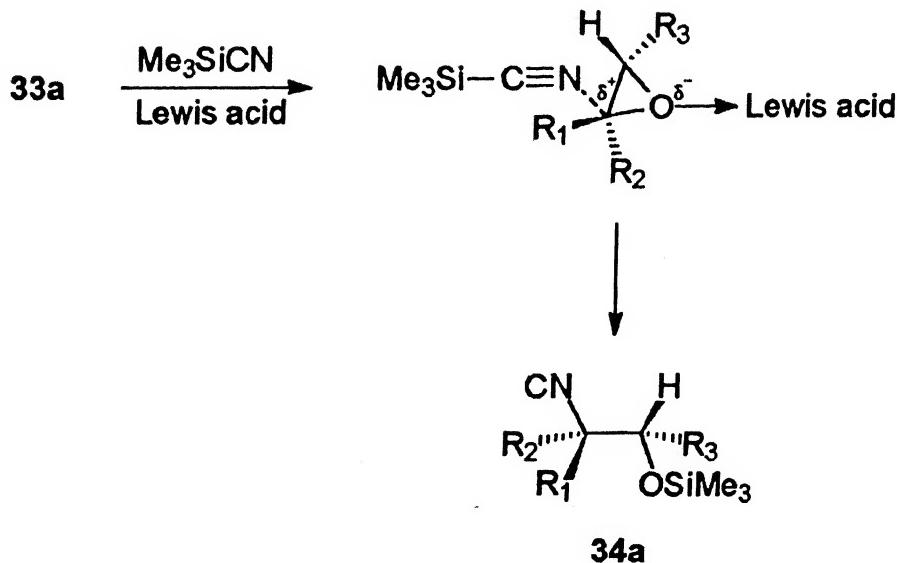
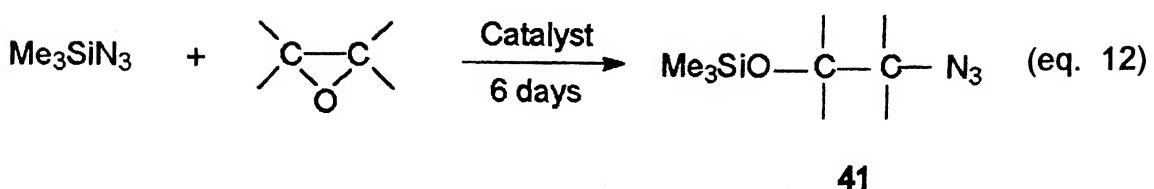
**Scheme 4.9**

catalyst :  $\text{Pd}(\text{CN})_2$ ,  $\text{SnCl}_2$ ,  $\text{Me}_3\text{Ga}$

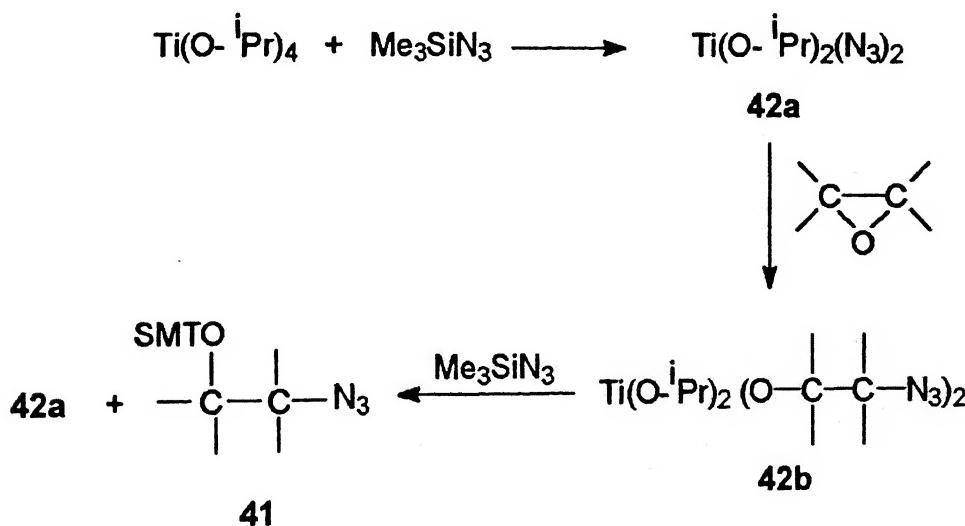
oxygen and more substituted carbon and (2) weakly nucleophilic TMS-CN attacks the more electrophilic site of the activated oxiranes (Scheme 4.10).

Vicinal azidohydrins which are potential precursors for  $\beta$ -amino alcohols are generally obtained from epoxides by the reaction with an alkali azide. During the last decade, the combined use of trimethylsilyl azide or sodium azide and a Lewis acid or a transition-metal complex has been successfully applied to the ring-opening of epoxides and 2,3-epoxy-alcohols.

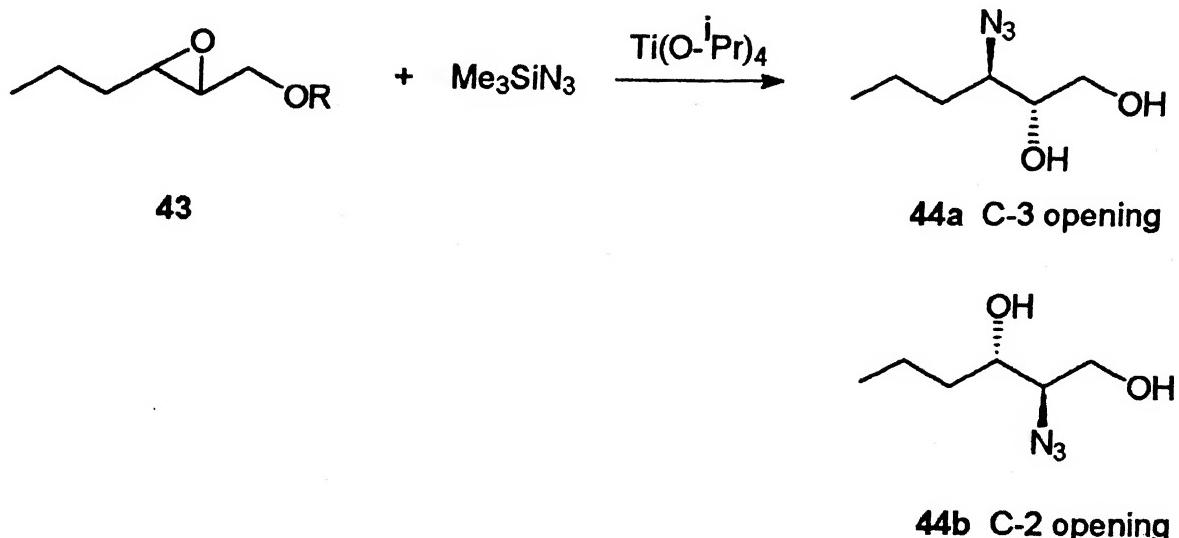
$\text{O}$ -protected vicinal azidohydrins 41 can be synthesized by the reaction of an oxirane with trimethyl silyl azide in the presence of titanium or vanadium complexes<sup>24</sup> (eq. 12). The one pot reaction takes place under very mild conditions in quantitative yield.

**Scheme 4.10**

In these reactions the transition metal azide **42a** is formed first and the second step is the insertion of the epoxide into the M-N<sub>3</sub> bond (Scheme 4.11). This azido-alkoxy group **42b**

**Scheme 4.11**

can be readily substituted by reaction with  $\text{Me}_3\text{SiN}_3$  to give the product. 2,3-epoxy alcohols **43** react with  $\text{Me}_3\text{SiN}_3$  in the presence of  $\text{Ti}(\text{O-i-Pr})_4$  to afford azido diols<sup>25</sup> **44a-b** in a C-3 to C-2 ratio of 14:1 in good yields (Scheme 4.12).



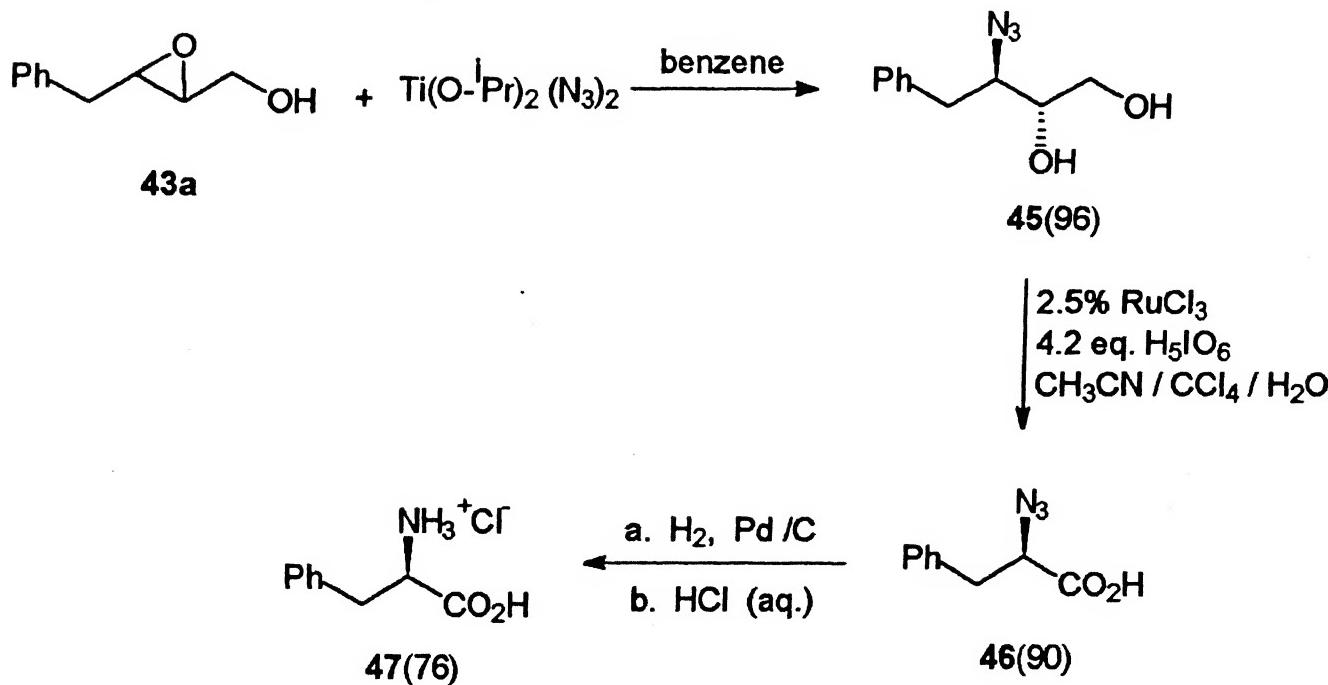
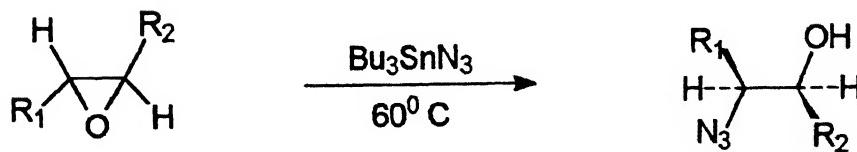
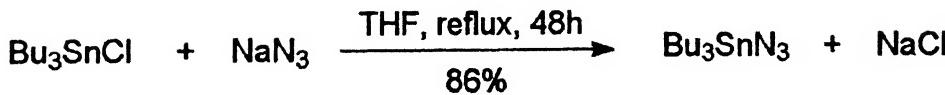
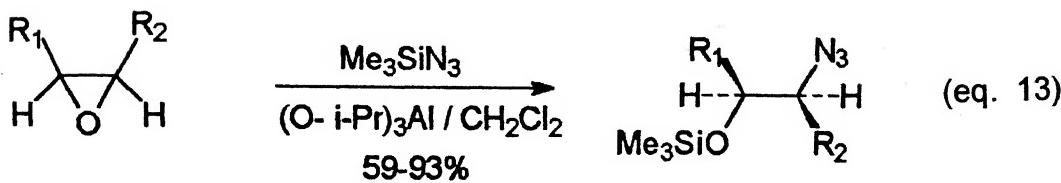
**Scheme 4.12**

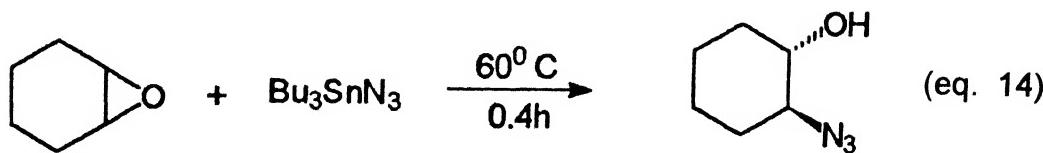
Treatment of 2,3-epoxy alcohols with  $[\text{Ti}(\text{O-i-Pr})_2(\text{N}_3)_2]$  **42a** affords the corresponding 3-azido 1,2-diols<sup>26</sup>, which are readily transformed in two steps to the  $\alpha$ -amino acids (Scheme 4.13). The  $[\text{Ti}(\text{O-i-Pr})_2(\text{N}_3)_2]$  reagent **42a** can be prepared according to the procedure published by Choukroun and Gervais<sup>27</sup>.

Cyclic epoxides react with trimethylsilyl azide in the presence of a catalytic amount of aluminium isopropoxide to give stereospecifically trans trimethylsilyloxy azides in good yields<sup>28</sup> (eq. 13). Unsymmetrical epoxides showed high regioselectivity and chemospecificity, only the primary azide was obtained in good yield.

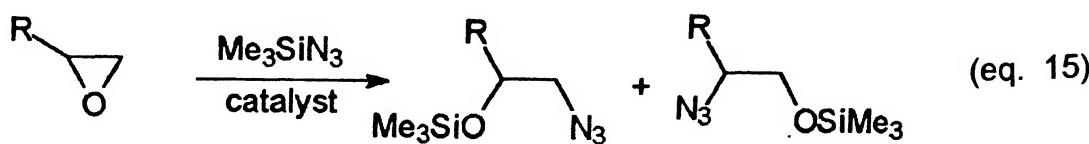
Oxirane ring cleavage also can occur with tributyltin azide to provide 1,2-azido alcohols in good to excellent yields<sup>29</sup>. Tributyltin azide<sup>30</sup> can be prepared with tributyltin chloride and sodium azide in THF (Scheme 4.14). For example, trans- 2-azido cyclohexanol **48** can be prepared from cyclohexene oxide and TBT-N<sub>3</sub> in the absence of solvent (eq. 14).

Sinou and coworkers<sup>31</sup> have reported that the highly regioselective ring opening of epoxides with  $\text{Me}_3\text{SiN}_3$  in the presence of catalytic amount of titanium tetraisopropoxide and

**Scheme 4.13****Scheme 4.14**

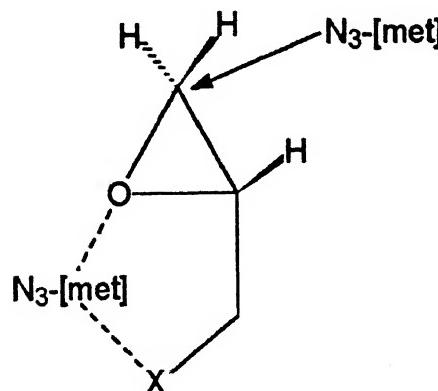


aluminium isopropoxide. Epoxides bearing an electron-withdrawing group at C-3 position are regiospecific, the attack of nucleophile occurs at C-3 position (eq. 15).



$R = HOCH_2, CH_2OCH_2,$   
 $t\text{BuOCH}_2, AcOCH_2, Cl, Br.$

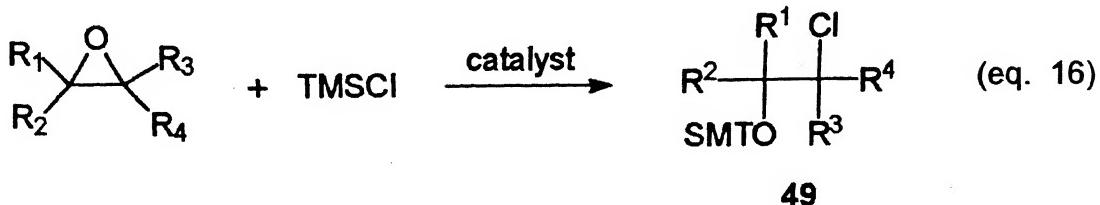
The highly regioselective ring opening of these functionalized epoxides by  $Ti(O-i-Pr)_4$  or  $Al(O-i-Pr)_3$  could be rationalized by invoking the formation of a coordinated structure around the metal centre<sup>32,33</sup> (Scheme 4.15). Opening at C-3 could occur preferentially because of formation of a stable five membered chelation structure, instead of a six membered chelation structure, which seems less stable, for the opening at C-2 position.



**Scheme 4.15**

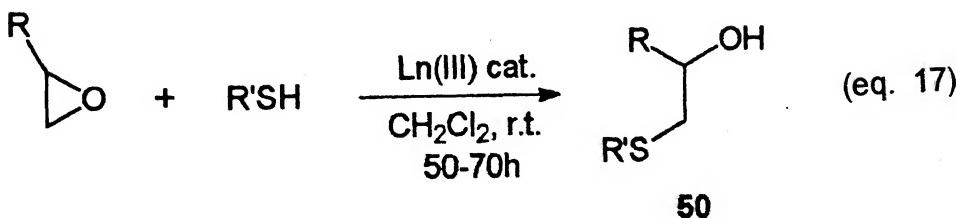
Regioselective cleavage of oxiranes by halosilanes<sup>34</sup> is an extremely mild and useful method for gaining access to O-silylated vicinal halohydrins. Bromo and Iodo trimethylsilanes cleave oxiranes without a catalyst whereas nucleophilic catalyst is required if chlorotrimethylsilane is used for such a cleavage.

Silicon halides in the presence of nucleophilic catalyst react with epoxides to form O-protected vicinal halohydrins **49** in quantitative yields with enhanced regioselectivity under extremely mild conditions<sup>35,36</sup> (eq. 16). The catalysts used in this ring opening reactions are tetra-n-butyl ammoniumchloride and triphenylphosphine.

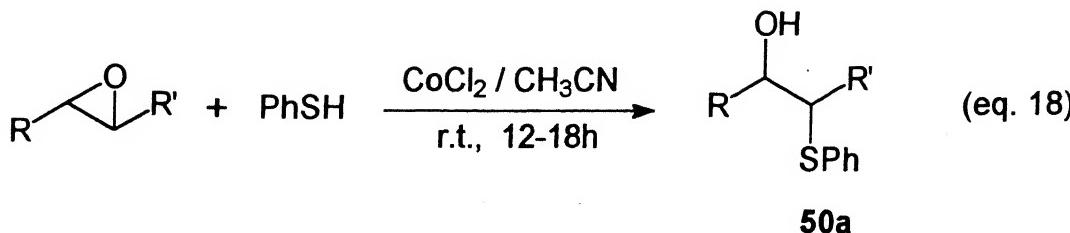


The formation of primary chloride in the reactions with styrene oxide and butadiene monooxide and of trans O-trimethylsilyl vicinal chlorohydrins with cyclohexene and cyclopentene oxide suggests the mechanism for the insertion to involve a nucleophilic opening of the epoxide rather than a four center insertion into the carbon-oxygen bond<sup>37</sup>.

Epoxide ring can also be opened by sulfur nucleophiles. Kagan and coworkers<sup>38</sup> have reported that anhydrous lanthanide trichlorides which are considered as hard acids<sup>39</sup> catalyze the oxirane ring opening reaction with thiols stereo- or regio-selectively under mild conditions (eq. 17). Lanthanide catalysts used here are SmCl<sub>3</sub>, CeCl<sub>3</sub> and Eu(fod)<sub>3</sub> [tris-(6,6,7,7,8,8,8-heptafluoro-2,2,-dimethyl-3,5-octanedionato) europium(III)].



Recently in our laboratory it has been shown<sup>40</sup> that oxiranes can be regioselectively cleaved by benzenethiol in the presence of cobalt(II) chloride or  $\text{Co}_2(\text{CO})_8$  to the corresponding  $\beta$ -hydroxy sulfides **50a** in good yields (eq. 18).



## 4.5 PRESENT STUDY

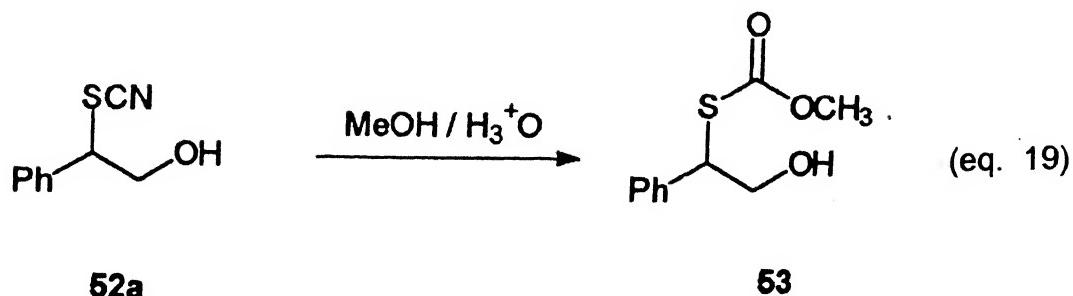
The previous section has clearly highlighted that epoxides are versatile intermediates during organic synthesis. They can be cleaved with wide range of carbon and heteroatom nucleophiles to give useful precursors for large number of natural products. We have explored the catalytic opening of epoxides with silicon based reagents and the following section deals with our results.

We have observed that cobalt(II) chloride is an efficient catalyst for the opening of epoxides with trimethylsilyl thiocyanate. Thus wide range of epoxides undergo smooth cleavage with *in situ* generated trimethylsilyl thiocyanate (obtained by exchange reaction between trimethylsilyl chloride and sodium thiocyanate in acetonitrile) to give one regioisomer. Styrene oxide **51a** and 1,2-epoxybutane **51b** provided mainly one regioisomer, **52a** and **52b** respectively whereas, epichlorohydrin **51c** showed poor regioselectivity (Table 4.6, entries 1-3). The cleavage of cyclohexene oxide **51d** took place stereoselectively to give mainly the trans diastereomer **52d** (Table 4.6, entry 4). Interestingly, glycidyl methacrylate **51e** also underwent highly chemoselective epoxide opening to give the equal mixture of regioisomers **52e** (Table 4.6, entry 5). Opening of epoxide with thiocyanate unprecedented and thus this methodology provides an efficient route to this class of compounds.

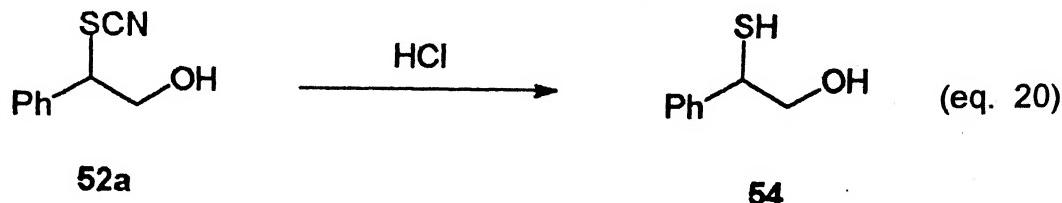
The chemoselectivity of this compound was confirmed by hydrolysis of hydroxy thiocyanate **52a** to the corresponding thiocarbonate **53** (eq. 19).

**Table 4.6 : Cobalt (II) Catalysed Opening of Epoxides with Trimethyl Silyl Thiocyanate.**

Entry	Epoxides	Products(yield%)	
1			
	<b>51a</b>	<b>52a(85)</b>	90:10
2			
	<b>51b</b>	<b>52b(81)</b>	75:24
3			
	<b>51c</b>	<b>52c(79)</b>	60:40
4			
	<b>51d</b>	<b>52d(87)</b>	
5			
	<b>51e</b>	<b>52e(65)</b>	50:50

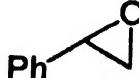
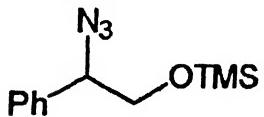
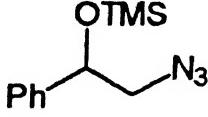
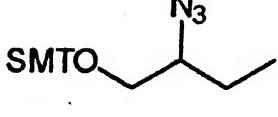
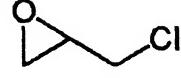
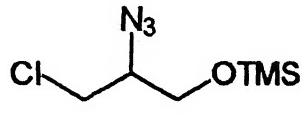
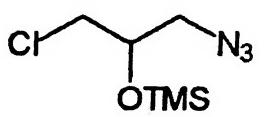
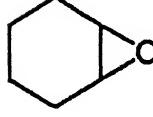
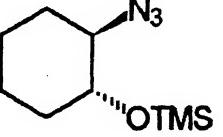
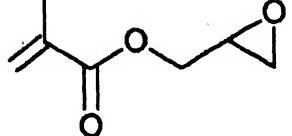
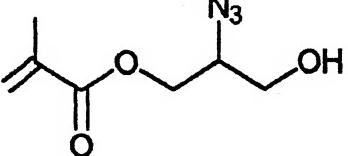
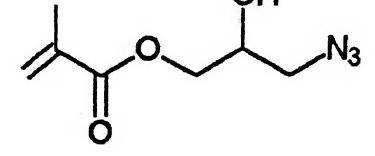
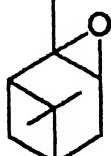
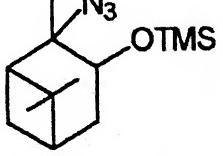
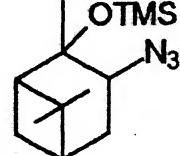


Further evidence for this was also obtained by acid hydrolysis of hydroxy thiocyanate **52a** to give hydroxy thiol **54** (eq. 20). These experiments clearly reveal that these compounds are hydroxy thiocyanates rather than hydroxy isothiocyanates.



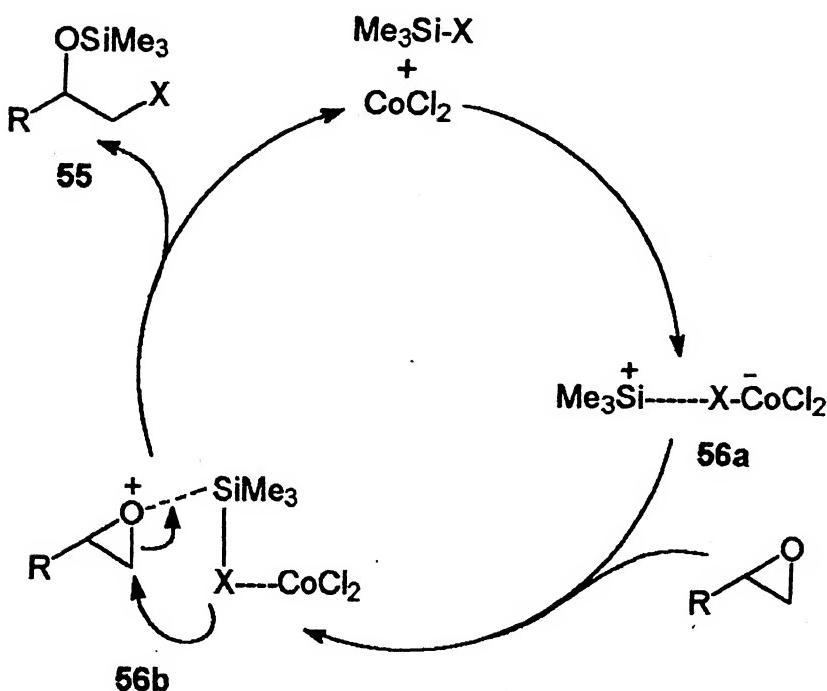
We have also explored the cobalt(II) chloride catalyzed cleavage of oxiranes with *in situ* generated trimethylsilyl azide (generated by exchange between trimethylsilyl chloride and sodium azide in DMF) to give the O-silylated azides (table 4.7). The reaction of styrene oxide **51a** and 1,2-epoxybutane **51b** with trimethylsilyl azide and cobalt chloride in DMF afforded high yield of  $\beta$ -azido trimethylsilyl ethers **55a-b** (Table 4.7, entries 1 and 2). Poor selectivity was observed in these reactions except for the reaction with epichlorohydrin **51c** which gave one regioisomer **55c** as major product (Table 4.7, entry 3). Cyclohexene oxide **51d** was cleaved in stereoselective manner to give trans-trimethylsilyl azide ether **55d** as the only product (Table 4.7, entry 4). Cleavage of pinene oxide **51f** could be carried out in good yields with poor regioselectivity (Table 4.7, entry 5). Similarly, glycidyl methacrylate **51e** underwent smooth cleavage to give equal mixture of regioisomers **55e** (Table 4.7, entry 6). Interestingly, the products derived from glycidyl methacrylate **51e** could not be isolated as trimethylsilyl ethers as they readily underwent hydrolysis to the corresponding alcohols. This method of cleavage of epoxide by trimethylsilyl azide has the advantage over the titanium promoted cleavage as in the latter case stoichiometric amount of titanium complex is required.

**Table 4.7 : Cobalt (II) Catalysed Opening of Epoxides with Trimethyl Silyl Azide.**

Entry	Epoxides	Products(yield%)	
1	 <b>51a</b>		 <b>55a(87) 40:60</b>
2	 <b>51b</b>		 <b>55b(82) 35:65</b>
3	 <b>51c</b>		 <b>55c(79) 15:85</b>
4	 <b>51d</b>		 <b>55d(91)</b>
5	 <b>51e</b>		 <b>55e(62) 50:50</b>
6	 <b>51f</b>		 <b>55f(68) 55:45</b>

It also has the advantage over the other similar transformations because this transformation may be achieved by *in situ* generated trimethylsilyl azide. So our methodology seems better than the existing ones.

Mechanistically this reaction is proceeding via an initial formation of trimethylsilyl cation **56a** which may facilitate the opening of epoxide ring via coordination (Scheme 4.16).

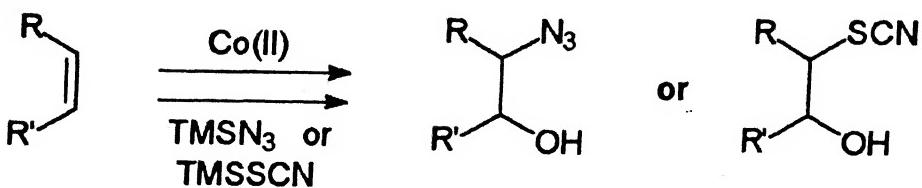


Scheme 4.16

The formation of trimethylsilyl cation **56a** may be favored due to the coordination of **CoCl<sub>2</sub>** in acetonitrile. A similar observation has been made earlier for the formation of a silicon cation from **Cl-SiMe<sub>3</sub>** in the presence of cobalt.

In conclusion, we have demonstrated that trimethylsilyl thiocyanate and azide are useful reagents for opening of epoxide in the presence of catalytic quantity of cobalt chloride. This methodology is quite efficient as it can be performed in high yields. Although the regioselectivity of these reactions are modest but mild and simple operation conditions will make it a useful synthetic method.

Finally, we have shown in this chapter that cobalt(II) is a versatile catalyst for the formation as well as reactivity of epoxides. The overall transformation described in this chapter may be depicted as conversion of alkene to hydroxy thiocyanates and azides.



## 4.6 EXPERIMENTAL

### General Procedure for the synthesis of hydroxy thiocyanate

Sodium thiocyanate (12 mmol) was taken in dry acetonitrile (50 mL). Trimethylsilyl chloride (10 mmol) was added at 0° C and stirred for 0.5h. Catalytic amount of CoCl<sub>2</sub> (~50 mg) and epoxide (10 mmol) was added and the reaction mixture was stirred for 1h at room temperature, then heated at 70° C for 5-10h. Solvent was evaporated on vacuo, the residue was taken in ethylacetate (50 mL), washed with saturated sodium bicarbonate (4x30 mL), water (2x30 mL) and brine (1x30 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation of the solvent afforded a residue which was subjected to column chromatography to afford the hydroxy thiocyanate in high yield.

### 1-Phenyl 2-hydroxy ethane 1-thiocyanate 52a

Styrene oxide 51a (1.20g, 10 mmol), sodium thiocyanate (0.97g, 12 mmol), TMSCl (1.08g, 10 mmol) and CoCl<sub>2</sub> (~50 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by the column chromatography afforded 52a (1.52g, 85%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 7.35 (s, 5H), 4.5 (t, J = 6.25 Hz, 1H), 4.1 (d, J = 7.5 Hz, 2H), 2.78 (br s, 1H).

IR (Thinfilm) : ν<sub>max</sub> 3400, 3040, 2140, 1480, 1160, 1050 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>9</sub>NOS : C, 60.35; H, 5.02.

Found : C, 60.44; H, 5.11.

### 1-Hydroxy butane-2-thiocyanate 52b

1,2-Epoxybutane 51b (1.08g, 15 mmol), sodium thiocyanate (1.46g, 18 mmol), TMSCl (1.63g, 15 mmol) and CoCl<sub>2</sub> (~70 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded 52b (1.59g, 81%) as a mixture of regioisomers in 3:1 ratio.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : δ 4.0-3.75 (m, 1H), 3.16 (d, J = 6.25 Hz, 2H), 2.5 (br s, 1H), 1.8-1.5 (m, 2H), 1.0 (t, J = 7.5 Hz, 3H).

Anal. Calcd. for  $C_5H_9NOS$  : C, 45.82; H, 6.86.

Found : C, 45.94; H, 6.90.

### **1-Chloro 3-hydroxy propane-2-thiocyanate 52c**

Epichlorohydrin **51c** (1.39g, 15 mmol), sodium thiocyanate (1.46g, 18 mmol), TMSCl (1.63g, 15 mmol) and  $CoCl_2$  (~50 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **52c** (1.79g, 79%) as a mixture of two regioisomers in 3:2 ratio.

$^1H$ -NMR ( $CCl_4$ ) :  $\delta$  4.1-3.65 (m, 1H), 3.25 (d,  $J = 7.5$  Hz, 2H), 3.0 (d,  $J = 4.5$  Hz, 2H), 2.5 (br s, 1H).

IR (Thinfilm) :  $\nu_{max}$  2150, 1250, 1100, 830  $cm^{-1}$ .

Anal. Calcd. for  $C_4H_6ClNOS$  : C, 31.70; H, 3.94.

Found : C, 31.92; H, 4.02.

### **2-Hydroxy cyclohexyl thiocyanate 52d**

Cyclohexene oxide **51d** (1.47g, 15 mmol), sodium thiocyanate (1.46g, 18 mmol), TMSCl (1.63g, 15 mmol) and  $CoCl_2$  (~50 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup followed by column chromatography afforded **52d** (2.05g, 87%).

$^1H$ -NMR ( $CDCl_3$ ) :  $\delta$  3.78-3.40 (m, 1H), 3.18-2.75 (m, 2H), 2.43-1.25 (m, 8H).

IR (Thinfilm) :  $\nu_{max}$  3500, 2200, 1470, 1100  $cm^{-1}$ .

Anal. Calcd. for  $C_7H_{11}NOS$  : C, 53.52; H, 7.00.

Found : C, 53.67; H, 7.04.

### **Compound 52e**

Glycidyl methacrylate **51e** (1.42g, 10 mmol), sodium thiocyanate (0.78g, 12 mmol), TMSCl (1.08g, 10 mmol) and  $CoCl_2$  (~50 mg) in dry acetonitrile (50 mL) were subjected to the reaction conditions as described above. The usual workup afforded **52e** (1.30g, 65%) as a mixture of regioisomers in 1:1 ratio.

$^1H$ -NMR ( $CDCl_3$ ) :  $\delta$  5.8 (s, 1H), 5.3 (s, 1H), 4.0 (m, 2H), 3.5 (d,  $J = 7.0$  Hz, 2H), 3.0-2.6

IR (Thinfilm) :  $\nu_{max}$  3450, 2140, 1710, 1150  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_8\text{H}_{11}\text{NO}_3\text{S}$  : C, 47.78; H, 5.47.

Found : C, 47.98; H, 5.54.

### General Procedure for the Synthesis of O-Silylated Azidohydrins

Sodium azide (12 mmol) was taken in DMF (30 mL), trimethylsilylchloride (10 mmol) was added at 0° C and stirred for 0.5 hrs. Catalytic amount of  $\text{CoCl}_2$  (~30 mg) and epoxide (10 mmol) was added and the reaction mixture was stirred for 1 hr at room temperature, then heated at 70° C for 5-8 h. The reaction mixture was poured into 200g crushed ice extracted with ethyl acetate (3x50mL). The organic layer was washed with water (6x30 mL) finally with brine (1x50mL). Drying ( $\text{MgSO}_4$ ) and evaporation of the solvent yielded the O-silylated vicinal azidohydrins as a mixture of regioisomers. The ratio of the regioisomers was conformed by  $^1\text{H-NMR}$ .

Deprotection of silylated group was carried by taking the reaction mixture in dioxane (15 mL) and 20% HCl (15 mL) and stirred for 2h. Organic layer was taken into ethylacetate (50 mL) washed with saturated  $\text{NaHCO}_3$  solution (4x20 mL), water (2x20 mL) and brine (1x20 mL). Drying ( $\text{MgSO}_4$ ) and evaporation of the solvent afforded vicinal azidohydrins in high yields.

#### 1-Trimethylsilyloxy 1-phenyl 2-azido ethane 55a

Styrene oxide **51a** (1.20g, 10 mmol), sodium azide (0.78g, 12 mmol), TMSCl (1.08g, 10 mmol) and catalytic amount of  $\text{CoCl}_2$  (30 mg) in DMF (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **55a** (2.04g, 87%) as a colourless liquid.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  7.1 (s, 5H), 4.8-4.25 (m, 1H), 3.55 (d,  $J = 7.0$  Hz, 2H), 0.15 (s, 9H).

IR (Thinfilm) :  $\nu_{max}$  3080, 2120, 1250  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{17}\text{N}_3\text{OSi}$  : C, 56.18; H, 7.23; N, 17.86.

Found : C, 56.32; H, 7.31; N, 17.97.

**1-Azido 2-trimethylsilyloxy butane 55b**

1,2-Epoxy butane **51b** (1.08 g, 15 mmol), sodium azide (1.17g, 18 mmol), TMSCl (1.63g, 15 mmol) and CoCl<sub>2</sub> (~30 mg) in DMF (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **55b** (2.30g, 82%) as a mixture of two regioisomers in 2.5:1 ratio.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  3.6-3.2 (m, 1H), 2.9 (d, J = 7.0 Hz, 2H), 1.5-1.1 (m, 2H), 0.8 (m, 3H), 0.15(s, 9H).

IR (Thinfilm) :  $\nu_{max}$  2100, 1250 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>7</sub>H<sub>17</sub>N<sub>3</sub>OSi : C, 44.92; H, 9.08.

Found : C, 45.05; H, 9.14.

**1-Azido 2-trimethylsilyloxy 3-chloro propane 55c**

Epichlorohydrin **51c** (1.39g, 15 mmol), sodium azide (1.17g, 18 mmol), TMSCl (1.63g, 15 mmol) and CoCl<sub>2</sub> (~50 mg) in DMF (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **55c** (2.64g, 85%) as a mixture of regioisomers in 4:1 ratio.

<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  4.0-3.65 (m, 1H), 3.5-3.1 (m, 4H), 0.1(s, 9H).

IR (Thinfilm) :  $\nu_{max}$  2100, 1250 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>6</sub>H<sub>14</sub>ClN<sub>3</sub>OSi : C, 34.72; H, 6.74.

Found : C, 34.92; H, 6.80.

**1-trimethylsilyloxy 2-azido cyclohexane 55d**

Cyclohexene oxide **51d** (1.47g, 15 mmol), sodium azide (1.17g, 18 mmol), TMSCl (1.63g, 15 mmol) and CoCl<sub>2</sub> (~30 mg) in DMF (30 mL) were subjected to the reaction conditions as described above to afford **55d** (2.90g, 91%).

<sup>1</sup>H-NMR (CCl<sub>4</sub>) :  $\delta$  3.45-3.0 (m, 2H), 2.2-1.0 (m, 8H), 0.15 (s, 9H).

IR (Thinfilm) :  $\nu_{max}$  2100, 1250 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>9</sub>H<sub>19</sub>N<sub>3</sub>OSi : C, 50.72; H, 8.91.

Found : C, 50.79; H, 8.97.

**Compound 55f**

$\alpha$ -Pinene oxide **51f** (1.52g, 10 mmol), sodium azide (0.78g, 12 mmol), TMSCl (1.08g, 10 mmol) and  $\text{CoCl}_2$  ( $\sim$ 30 mg) in DMF (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **55f** (1.81g, 68%) as a mixture of regioisomers in 1:1 ratio.

$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  3.9-3.6 (m, 1H), 2.0-1.8 (m, 2H), 1.5-0.65 (m, 13H) 0.2(s, 9H).

IR (Thinfilm) :  $\nu_{max}$  2100, 1250  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{13}\text{H}_{25}\text{N}_3\text{OSi}$  : C, 58.44; H, 9.35.

Found : C, 58.62; H, 9.43.

**Compound 55e**

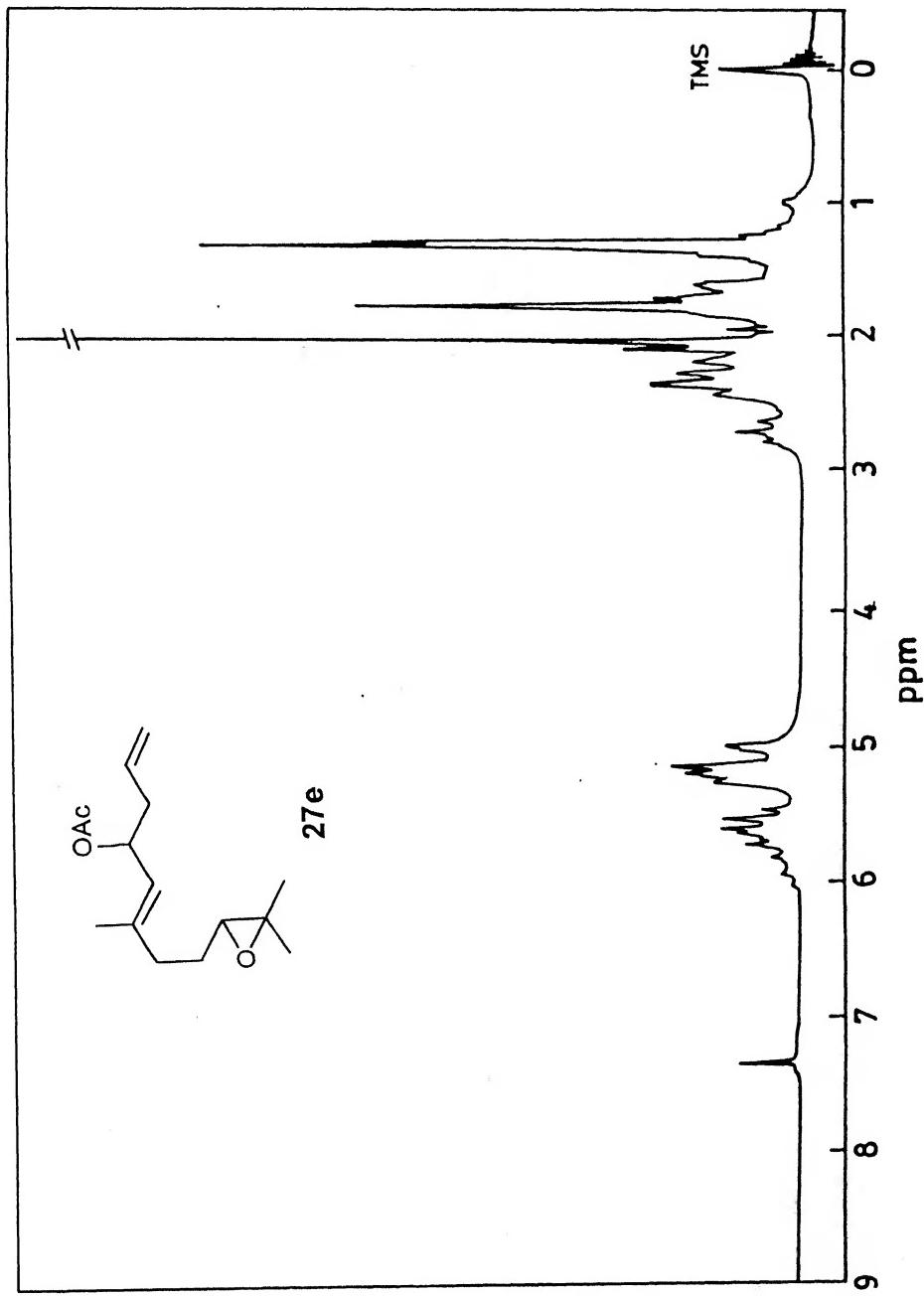
Glycidyl methacrylate **51e** (1.42g, 10 mmol), sodium azide (0.78g, 12 mmol), TMSCl (1.08g, 10 mmol) and  $\text{CoCl}_2$  ( $\sim$ 50 mg) in DMF (30 mL) were subjected to the reaction conditions as described above. The usual workup afforded **55e** (1.14g, 62%).

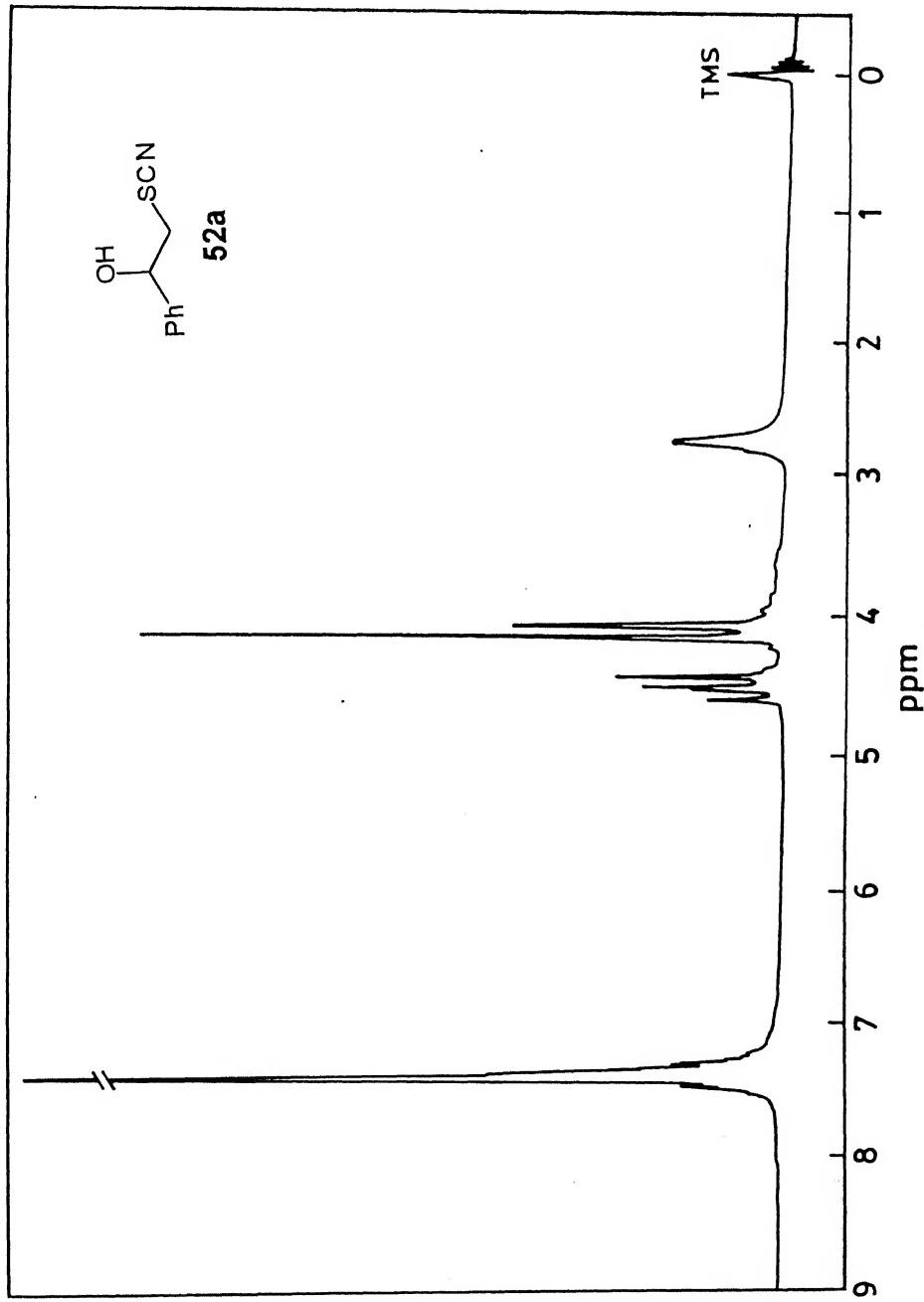
$^1\text{H-NMR}$  ( $\text{CCl}_4$ ) :  $\delta$  5.8 (s, 1H), 5.3 (s, 1H), 4.0 (m, 2H), 3.7 (m, 1H), 2.9 (br s, 1H), 2.6-2.2 (m, 2H), 1.75 (s, 3H).

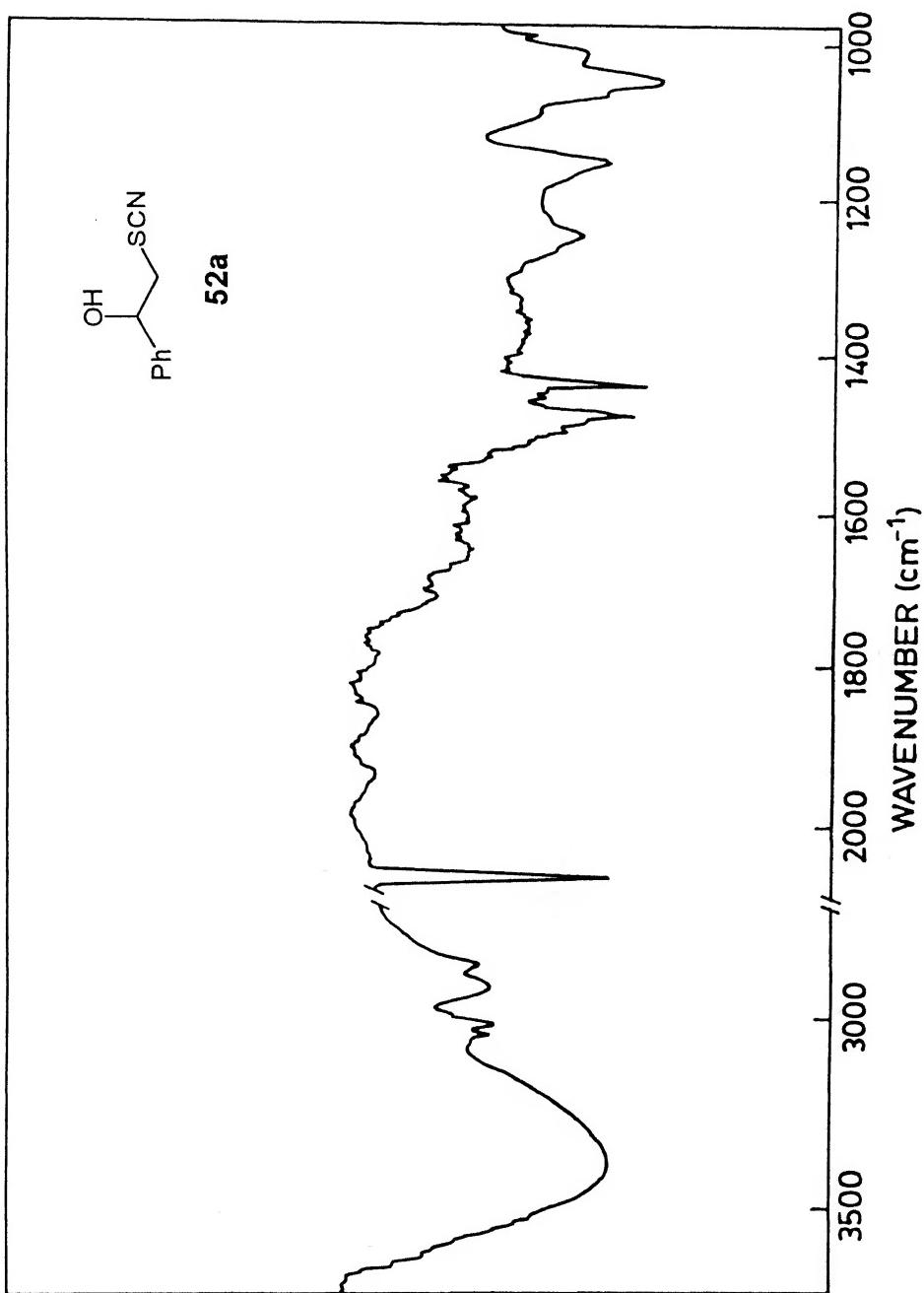
IR (Thinfilm) :  $\nu_{max}$  3500, 2100, 1720, 1640, 1250  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_7\text{H}_{11}\text{N}_3\text{O}_3$  : C, 45.42; H, 5.94.

Found : C, 45.51; H, 5.96.







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## List of Publications

1. Cobalt(II) Chloride Catalysed Conversion of Allylic Alcohols to Rearranged Allylic Amides.  
Nayyar, N. K., **Reddy, M. M.** and Iqbal, J. *Tet. Lett.* **1991**, 32, 6965.
2. Cobalt(II) Complex Catalysed Epoxidation with Molecular Oxygen.  
Iqbal, J. , Bhatia, S. and **Reddy, M. M.** *Syn. Commun.*, **1993**, 2285.
3. Cobalt(II) catalysed allylation of 1,3-dicarbonyl compounds with allyl acetates.  
Bhatia, B, **Reddy, M. M.** and Iqbal, J. *Tet. Lett.* **1993**, 34, 6301.
4. Cobalt catalyzed three component coupling involving ketones or ketoesters, aldehydes and acetonitrile: A novel one pot synthesis of  $\beta$ -acetamido ketones.  
Bhatia, B.,**Reddy, M. M.** and Iqbal, J. *J. J. Chem. Soc. Chem. Commn.*, (in press).
5. Cobalt(II) Catalysed Conversion of Allylic Alcohols to Transposed Allylic Amides in the Presence of Nitriles.  
**Reddy, M. M.**, Maikap, G. C. and Iqbal, J. *under preparation*.
6. Cobalt Catalysed Regioselective Allylation of 1,3- Dicarbonyl Compounds.  
**Reddy M. M.**, Manoj M., Maikap G. C. Bhatia B., Iqbal J. *Tetrahedron* **1994**, communicated.

Several other manuscripts are under preparation.